A MIXED METHODS ANALYSIS OF *CLOSTRIDIOIDES DIFFICILE* INFECTION AND IMPLEMENTATION OF A QUALITY IMPROVEMENT INTERVENTION IN PUBLIC SECTOR HOSPITALS IN CAPE TOWN, SOUTH AFRICA

LAUREL LEGENZA

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Supervisor: Professor Renier Coetzee

Co-supervisors: Doctor Susanne Barnett & Doctor Warren Rose

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KEYWORDS

Clostridioides difficile

C. difficile infection (CDI)

Epidemiology

Infectious diseases

Healthcare associated infection

Infection prevention and control

Antimicrobial stewardship

Quality improvement

Implementation science

Public sector

ABSTRACT

A MIXED METHODS ANALYSIS OF *CLOSTRIDIOIDES DIFFICILE* INFECTION AND IMPLEMENTATION OF A QUALITY IMPROVEMENT INTERVENTION IN PUBLIC SECTOR HOSPITALS IN CAPE TOWN, SOUTH AFRICA

L. Legenza

PhD Thesis, School of Pharmacy, University of the Western Cape

Background: *Clostridioides difficile* or *Clostridium difficile* infection (CDI), is a global health threat known for devastating outbreaks, high-cost complications, readmissions and mortality. While CDI is widely studied in high resource settings, existing literature neglects low resource settings. Prior to this study, no publications were available on the epidemiology of CDI and CDI patient outcomes in the secondary hospitals in the public healthcare sector — gaps this thesis addresses. No publications existed on provider awareness of CDI and CDI management workflow in sub-Saharan Africa.

This thesis aims to a) determine baseline CDI patient characteristics, management of and contribution to mortality in SA, b) identify CDI perceptions and practices among healthcare providers in SA secondary hospitals, including facilitators and barriers to providing quality CDI care, and c) develop a CDI intervention and analysis thereof.

Methods: This thesis used a mixed methods approach, with qualitative interview data and quantitative epidemiology and patient outcomes data. The study included a retrospective review of patients tested for *C. difficile* across four public district hospitals in the greater Cape Town metropole. Then, the study developed a CDI intervention with Expert Recommendations for Implementing Change strategies and local context gathered from the study data. The Consolidated Framework for Implementation Research (CFIR) and the Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies were applied to collected data and

observations to identify drivers and barriers to implementing and understanding differences in intervention uptake.

Results: A novel risk factor for CDI was identified and associated mortality risk was documented. In this population with high tuberculosis (TB) and human immunodeficiency virus comorbidity, TB was an additional risk factor. Mortality of patients with a *C. difficile* positive result was higher than similar patients testing negative with diarrhoea (29% versus 8%, $p < 0.0001$). While most treated patients received metronidazole, this study recommended that vancomycin should be considered as an alternative to metronidazole in populations with high prevalence of TB and immunocompromised conditions. The study uncovered healthcare provider knowledge gaps in identifying, diagnosing, treating and preventing CDI. Many providers were unaware of CDI characteristics. This study's results showed opportunities to improve CDI management. The resulting intervention and implementation package included a CDI checklist and provider education. One of the three hospitals displayed high intervention uptake. Analysis of the intervention and implementation found relevant CFIR constructs linked to intervention uptake: tension for change, strong peer intervention champions, champions in influential leadership positions, and the intervention's simplicity (CFIR construct: complexity). Proactive adaptations to the champions strategy facilitated the implementation. Tension for change was supported by an academic partnership for antimicrobial stewardship at a high uptake hospital.

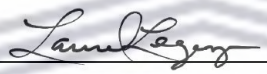
Conclusion: This thesis contributes baseline data on CDI epidemiology, treatment and outcomes; detailed facilitators and barriers to CDI care; and a contextualized CDI intervention. The intervention development and implementation analysis identified factors associated with the intervention's uptake. Thus, this study contributes to the fields of pharmacy, infectious diseases, and implementation science. This thesis underscores the need for intervening as patients are at high risk of CDI-associated mortality in SA.

December 2022

DECLARATION

I declare that *A mixed methods analysis of Clostridioides difficile infection and implementation of a quality improvement intervention in public sector hospitals in Cape Town, South Africa* is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full name: Laurel Legenza Date 10 December 2022

Signed: 

Witness

Full name: Professor Renier Coetzee Date 10 December 2022

Signed: 

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CONTENTS

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1 INTRODUCTION

Clostridioides difficile or *Clostridium difficile* infection (CDI), is an urgent global health threat. However, the extent of the infection and current practices of treating and preventing CDI are understudied in low resource settings.[1-8] Following massive CDI outbreaks across North America and Europe, evidence-based CDI interventions were developed and implemented to reduce the impact of CDI in high resource settings.[9] Comparatively, the epidemiology and outcomes of CDI in SA and other low to middle income countries (LMICs) is unknown.[5,10,11] Beyond this study, there are no published literature studies on managing CDIs and outcomes in low resource public district level hospitals in sub-Saharan Africa. Furthermore, facilitators and barriers to treating CDIs are unknown and critical to the effective design and study of interventions that fit the local context.

CDI is a global infectious disease problem that is associated with high-cost complications, readmissions and mortality.[6,12-14] Clinical presentation ranges from mild to severe diarrhoea and dehydration. CDI is associated with life-threatening complications, such as sepsis, kidney failure, toxic megacolon and bowel perforation. After an initial episode of CDI, patients have a 10% to 30% risk of recurrence. Patients may be colonised and asymptotic.[4]

At the beginning of the twenty-first century, CDI outbreaks closed hospital units and resulted in devastating complications and deaths in Europe and North America.[12,15,16] Today, CDI remains classified as an urgent threat by the Centers for Disease Control and Prevention (CDC) and the number of CDI cases reported in North American and European hospitals is reported and monitored.[3,12] CDI incidence following outbreaks in the 2000s continued to increase, until 2018 when recent reports suggested the control of the infection with interventions.[17] However, the disease is less understood and there are few published CDI studies from the developing world (which includes Africa and Latin America).[10,18,19] Hypervirulent *C. difficile* strains have been identified and described in Western countries and SA.[20,21] As identified by infectious disease physicians and pharmacists engaged

with this research, CDI is an area of needed research in hospitals in Cape Town, SA. In a prospective study of CDI incidence at a tertiary hospital in Cape Town, SA, 9.2% of patients admitted to the hospital with diarrhoea or who developed diarrhoea while hospitalised, were diagnosed with CDI.[21] This study is the first to describe the contributing factors and patient demographics of CDI in secondary hospitals in Cape Town, SA.

Health system strengthening, including improving the quality of care, is needed in developed and developing countries.[22-25] Addressing multiple components of the delivery of patient care at an institution (or the bundle approach), has been an effective model for improving healthcare quality, especially in reducing healthcare-associated infections.[26,27] Implementing a bundle checklist includes appropriate staff training on the checklist and rationale of listed tasks. Hospital checklists of CDI interventions (contact precautions, laboratory testing and treatment) have been implemented. However, research on CDI bundle effectiveness is less than research on individual interventions for other diseases and infection types (e.g., bundle interventions for central line-associated blood stream infections [CLABSI] and catheter-associated urinary tract infections [CAUTI]).[9,27] In order to address the need for more data on CDI in Cape Town and health system strengthening, a mixed-methods approach to describing CDI presents an opportunity to inform the development of an implementation package for both health system strengthening and improving outcomes.

1.1 Research focus

This study examines CDI in Cape Town, SA, using a mixed methods research to evaluate CDI epidemiology and management, to identify opportunities to improve the quality of care provided. The research describes the demographics and risk factors of CDI patients in SA, and outlines facilitators and barriers to managing CDI. This quantifies the characteristics of CDI patients in SA, the treatment and management measures provided as well as the patient outcomes. Furthermore, this study involves qualitatively uncovering how patients are identified and treated in

public district level hospitals via interviews and focus groups across disciplines. This study's focus on CDI aligns with the priorities outlined in the 2014–2024 SA Antimicrobial Resistance National Strategy Framework. This framework identifies the nation's commitment to promoting the appropriate use of antimicrobials through antimicrobial stewardship (AMS) (Strategic Objective 4).[28] CDI relates to AMS in that it:

- requires appropriate antibiotic therapy to be resolved, and
- can result from gut floral disruption from the overuse of antibiotics.[29-32]

The interdisciplinary focus of the research aligns with the Antimicrobial Resistance National Strategy Framework.[28] The study focuses on public district level hospitals. This is where the greatest need for data on Cape Town's CDI has been as identified by Department of Health (DoH) stakeholders, global infectious disease leaders based in Cape Town, and local SA healthcare providers. One of the few CDI studies in sub-Saharan Africa (specifically, Cape Town) was published at tertiary level.[21] Because SA has the greatest economic disparities in the world, stark socio-economic and health disparities exist in the Cape Town metropole.[33-35] The SA private sector has access to resources that are more like those of high resource settings. Meanwhile, the resources available in public district level hospitals are like other low resource healthcare settings across sub-Saharan Africa and other parts of the world. Thus, it is crucial that interventions consider the available resources.[36,37] Therefore, we purposefully chose to focus this research on public district level hospitals, so that the results and recommended interventions may be transferrable to other low resource settings.

First, the study's quantitative component focused on risk factors for SA CDIs compared to risk factors in high resource settings. The retrospective review included elements of care provided, when *C. difficile* laboratory tests were ordered, what treatment measures were taken as well as which infection prevention and control practices were documented. This quantitative assessment identified gaps in quality of care and identified areas of opportunity. Also, the results provided novel contributions on the epidemiology and outcomes of CDI in populations with high

prevalence of human immunodeficiency virus (HIV) and tuberculosis (TB). This is important because the impact of CDI in populations with high rates of HIV and TB is understudied. SA has the largest HIV epidemic in the world, with the greatest number of individuals living with HIV – 7.5 million people according to the 2021 Joint United Nations Programme on HIV/AIDS data.[38] Also, SA has high rates of TB co-infection in the HIV population. According to the 2019 Global Tuberculosis Report,[39] 59% of patients with TB (new and relapse) and a known HIV status were HIV positive in 2018. The SA patient population included here is a distinguishing component of this research.

Second, the study's qualitative component includes an interprofessional focus with interview and focus group discussions with various healthcare providers (physicians, nurses and pharmacists) and hospital administrators. The interviews and focus groups detail:

- How patients with symptoms and risk factors for CDI are identified,
- How and when a *C. difficile* test is ordered,
- How the results are found,
- Who orders treatment and management measures, and
- How measures of infection prevention and control are used.

Therefore, the research results can assist in defining facilitators and barriers to treatment and inform the development and implementation of a quality improvement intervention, with input from various healthcare providers.

Third, this research followed implementation science (IS) principles, a rapidly emerging field aimed at reducing the time from research results to translation into healthcare practice.[40,41] This study used IS terms, specifically Expert Recommendations for Implementing Change (ERIC) strategies, to describe the research approach to support reproducibility and scalability.[42] Accordingly, the guidelines for naming, defining and operationalising the early implementation strategies were followed. Then, future interventions and innovations can build on this early baseline study with implementation frameworks.

1.2 Problem statement

CDI epidemiology, outcomes and management data are virtually non-existent in the literature from district level hospitals. This baseline understanding is essential to developing quality improvement interventions that are tailored to the local context (in this case, Cape Town district hospitals). While CDI is extensively studied in high resource settings, a lack of data on CDI in low resource settings exists. Furthermore, quality improvement interventions that are designed to fit the local context of the public district level are needed. Also, reporting of the interventions in a way that is reproducible and examined with a theoretical framework is essential for sustainment and scalability.

1.3 Study aim

This study aims to:

- determine baseline CDI patient characteristics and management as well as their contribution to mortality in SA,
- identify CDI perceptions and practices among healthcare providers in SA secondary hospitals, including facilitators and barriers to providing quality CDI care, and
- develop a CDI intervention and analyse the intervention with a theoretical framework.

This study supports the development of CDI interventions that consider local patient and contextual factors.

1.4 Specific study objectives

Objective 1: Determine the epidemiology, outcomes and management of patients with diarrhoea and tested for CDI hospitalised at the district level in the Western Cape.

1a. Determine the risk factors for a *C. difficile* positive result compared with a *C. difficile* negative result.
1b. Determine the risk factors for mortality in SA patients in the Western Cape with diarrhoea.

Objective 2: Identify CDI perceptions and management practices among healthcare providers in SA secondary hospitals and uncover facilitators and barriers to providing quality CDI care.

2a. Analyse interview data through qualitative thematic analysis to uncover facilitators and barriers to providing quality CDI care.
2b. Analyse quantitative data on CDI management and identify opportunities for improving the treatment provided and prevention measures.

Objective 3: Contextualise the CDI intervention and study findings within a conceptual framework.

3a. Develop a CDI intervention informed by preliminary data and stakeholder feedback.
3b. Analyse the CDI intervention development, implementation process and adaptations with the ERIC strategies and the Consolidated Framework for Implementation Research (CFIR) framework.

Objective 4: Report the findings regarding CDI in SA with recommendations for further research.

4a. Report the findings regarding CDI epidemiology and outcomes with recommendations for further research.
4b. Report the findings regarding CDI perceptions and management with recommendations for further research.

1.5 Research question

Few publications regarding CDI in SA exist and currently no publications are available on the epidemiology and outcomes of CDI in the secondary hospitals in the public healthcare sector. The Standard Treatment Guidelines and Essential Medicines List for SA in place at the time of study development[43] list treatment options for antibiotic-associated diarrhoea, but do not provide guidance regarding testing, controlling infections and selecting antibiotics. Increasing concern about CDI has urged us to investigate the current risk factors for CDI at secondary level hospitals in Cape Town and understand the current workflow facilitators and barriers to develop quality improvement strategies to improve outcomes. Context-informed CDI interventions are needed for low resource settings and understanding of the factors associated with dissemination and implementation in SA.

1.6 Study significance

The observed rise of CDI in high resource settings and severe complications (including increased hospital stay and mortality) creates need for further investigation in South Africa. The rate of CDI in SA (9.2% of patients presenting to a tertiary hospital with diarrhoea) is below Western countries' rates (up to 25% of healthcare-associated diarrhoea). However, these rates cannot be compared because the types of studies conducted and the extent of CDI surveillance are unmatched.[21,44] Protocols for laboratory diagnostics such as the type of test used and frequency of testing vary between healthcare settings over time.[45] The testing variations (enzyme immunoassay tests or polymerase chain reaction [PCR]) can result in differences in sensitivity and specificity.[46] As overuse of antibiotics and use of broad spectrum antibiotics are the major risk factors for CDI, the problem could continue to grow in South Africa without intervention. Furthermore, SA's HIV population is at greater risk of poor outcomes and mortality as immunocompromised patients are at higher risk of multiple infections and may be unable to overcome concomitant infections.

This mixed methods thesis provides valuable and previously unknown insights on CDI regarding the epidemiology and outcomes of hospitalised patients with CDI and facilitators and barriers to CDI treatment and prevention. This research identifies gaps and opportunities in the treatment provided and healthcare provider perceptions, along with recommendations to improve the quality of care and inform health systems strengthening interventions. Such recommendations incorporate results from the epidemiology study in the Western Cape, and provider workflow and resources available in this setting as gleaned from the qualitative research. Improved CDI care will improve patient outcomes and reduce hospital-acquired CDI transmission and patient readmission rates. Distinct departments, healthcare providers and hospital administrators who have already received the results are the local AMS committee, internal medicine departments, clinical governance and hospital management.

This thesis demonstrates how a context-informed quality improvement CDI bundle intervention was designed and implemented, as well as factors associated with its uptake across three public sector district level hospitals. The results contribute to the emerging field of IS. The IS principles and strategies followed are presented with ERIC, and the intervention development and uptake are analysed with the theoretical CFIR framework.[42,47] The Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies (FRAME-IS) is used to provide a precise understanding of implementation adaptations made during the implementation process.[48] Applying these frameworks contextualizes the study's findings and provides a reproducible description of the intervention development, implementation and adaptations. These IS frameworks provide structure to this study to explain what worked with the CDI intervention and what aspects need to be revised.

In summary, this thesis is significant because it provides novel baseline data on how patients in SA are being treated for CDI and the associated outcomes that can be used to design and measure quality improvement interventions. This study provides a CDI bundle intervention that is informed by the local context and an analysis of

the intervention with IS frameworks. Together, these study components contribute to the long-term goal of improving health outcomes.

1.7 Key abbreviations

AMS	antimicrobial stewardship
ASP	antimicrobial stewardship programme
C. difficile	*Clostridioides difficile* (formerly, *Clostridium difficile*)
CDAD	*C. difficile* associated diarrhoea
CDC	Centers for Disease Control and Prevention
CDI	*C. difficile* infection
CAUTI	catheter-associated urinary tract infections
CLABSI	central line-associated blood stream infections
CFIR	Consolidated Framework for Implementation Research
DNA	deoxyribonucleic acid
DoH	Department of Health
EML	essential medicines list
ERIC	Expert Recommendations for Implementing Change
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
FIP	International Pharmaceutical Federation
FMT	faecal microbiota transplantation
FRAME-IS	Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HPS	Hospital Pharmacy Section
IDSA	Infectious Diseases Society of America
IPC	Infection Prevention and Control
IS	implementation science
LMICs	low to middle income countries
MDR(-TB)	Multidrug resistant (tuberculosis)

NHLS	National Health Laboratory
PCR	polymerase chain reaction
SA	South Africa
SEIPS	Systems Engineering Initiative for Patient Safety
SHEA	Society for Healthcare Epidemiology of America
STGs	Standard Treatment Guidelines
TB	Tuberculosis
UK	United Kingdom
US	United States
UWC	University of the Western Cape
WHO	World Health Organisation
XDR-TB	Extensively drug-resistant TB

1.8 Key terms

Antimicrobial resistance: The ability of a microorganism to withstand treatment with an antimicrobial drug.[49]

Antimicrobial stewardship (AMS)*:* A multidisciplinary, systematic approach to optimising the appropriate use of all antimicrobials to improve patient outcomes and limit resistant pathogens emerging while ensuring patient safety.[50]

Clostridioides difficile (***C. difficile****;* formerly, ***Clostridium difficile***): A spore forming bacteria that can colonise the colon and is often hospital-acquired. The spores are transmitted via the faecal-oral route and can survive for extended periods in the environment on objects and contaminated hands. The change in taxonomy was proposed in 2015, published in 2016 and later accepted by the Clinical Laboratory and Standards Institute in 2018.[1,2]

C. difficile **associated diarrhoea (CDAD)**: A term used for patients with symptomatic diarrhoea and laboratory evidence of *C. difficile*. CDAD has been used synonymously as a term for CDI in the literature.[51] *C. difficile* associated disease,

abbreviated CDAD, originates from the 1980s. CDI is a recent term that is favoured over CDAD. Regardless, diagnosis must consider symptoms and laboratory results.[4,52]

***C. difficile* infection (CDI)**: Patients are at increased risk of CDI and associated diarrhoeal disease after treatment with antibiotics that kill other bacteria but permit *C. difficile* to overgrow. CDI diarrhoea can lead to severe complications, including the need for a colectomy and death. The spores are transmitted via the faecal-oral route and can survive for extended periods in the environment on objects and contaminated hands. Diagnosis must consider symptoms and laboratory results.[4]

1.9 Thesis outline

This thesis aims to:

- establish a baseline of data on managing CDI and outcomes in low resource settings,
- explore healthcare provider CDI perceptions and practices, and
- develop a context-informed intervention and analyse its implementation.

This section provides a brief guide on the content included in each chapter.

Chapter 1 outlines the study's rationale, discussing the research's focus and the problem of a lack of CDI data in sub-Saharan Africa and low resource settings. This introductory chapter provides an overview of the study design and research scope. The study aim, objectives, research question and significance are described. Key abbreviations and terms are included. A thesis outline is provided.

Chapter 2 provides a literature review. First, a global to local review of CDI is given. The global review starts with a brief history of CDI, including outbreaks. Second, early literature on CDI and HIV is detailed as SA has a high prevalence of HIV. Third, the global review focuses on CDI in low resource settings, sub-Saharan Africa and SA. Fourth, the literature review details CDI treatment and guidelines

globally and in SA, including recent changes. Then, the literature review explores the intersecting fields that are pillars of this research: quality improvement in healthcare, care bundles and CDI care bundles as well as antimicrobial resistance and AMS and IS. Thus, this literature review frames the research conducted and highlights the gaps in the existing research that this thesis addresses.

Chapter 3 presents the study's research design, a mixed methods approach which uses quantitative and qualitative research methodology. This chapter provides detail on the research study design including IS strategies used. This chapter details the choice of the public health sector in SA as the research setting and relevant historical context. Then, the chapter details the methods applied and rationale for their use. The chapter concludes with ethics and funding information.

Chapters 4 through 6 present the research results. These chapters include duplications of the published manuscripts (Chapters 4 and 5) and published online ahead of print manuscript (Chapter 6) presenting the results. References are included in each results chapter as they are in the published and accepted manuscripts corresponding to each journal's referencing format. The three results chapters open with the publication's reasoning and attributes. Following each manuscript, the contributions of the publication to the thesis and implications are presented, including impact factor and notable articles citing the paper. The research tools, journal author guidelines and supplementary file for Chapter 6 are included in the thesis appendices.

Chapter 4 presents the results on CDI epidemiology and outcomes. The chapter manuscript is published as: Legenza L, Barnett S, Rose W, Bianchini M, Safdar N, Coetzee R. The epidemiology and outcomes of *Clostridium difficile* infection among hospitalised patients in South Africa: results of a multicenter retrospective study. *BMJ Global Health*. 2018;3:e000889. PMCID: PMC6058171.

Chapter 5 presents the results on healthcare provider CDI perceptions and practices in South Africa. The chapter manuscript is published as: Legenza L, Barnett S, Rose

W, Emmerling T, Peh KH, Safdar N, Coetzee R. *Clostridium difficile* infection perceptions and practices in South Africa. *Antimicrob Resist Infect Control*. 2018;7:125. PMCID: PMC6206849.

Chapter 6 presents the context-informed intervention and analyses its development and implementation. The chapter manuscript is accepted for publication in *Research in Social and Administrative Pharmacy.*
Legenza L, Coetzee R, Rose WE, Esack-Smart T, Crombie C, Mina M, Safdar N, Barnett SG. Application of Consolidated Framework for Implementation Research to improve *Clostridioides difficile* infection management in district hospitals. *Research in Social and Administrative Pharmacy.* 2022. Accepted for publication. Available online with early access.

Chapter 7 discusses the novel contributions and provides the conclusions. This chapter details novel contributions to understanding CDI risk factors and outcomes, CDI perceptions and practices in SA, and CDI intervention. Research limitations and research bias are noted. The discussion describes the transferability of the results globally to other low resource settings. The chapter provides summative implications from the study results and recommendations for CDI interventions in SA to improve CDI quality of care and outcomes.

2 LITERATURE REVIEW

The literature review chapter builds the case for CDI research in low resource settings and our decision to conduct this research in public district level hospitals in SA. Outside this thesis research, no studies have examined CDI risk factors, management, infection control and mortality among hospitalised patients in public hospitals in sub-Saharan Africa to our knowledge. Healthcare provider practices and perceptions of managing CDI are limited in low resource settings. No such provider studies exist in sub-Saharan Africa outside of this thesis to our knowledge.

First, the literature review provides a global to local review of CDI burden (Section 2.1). Broadly, this global review includes subsections on the historical emergence of CDI (Section 2.1.1), CDI and HIV (Section 2.1.2), and a review of CDI in low resource settings, closing with SA (Section 2.1.3). Second, the chapter details CDI treatment options and guidelines globally and in SA (Section 2.2). Then, the chapter reviews quality improvement in healthcare (Section 2.3) and care bundles as related to the thesis research, including recently published systematic reviews that have compiled evidence on quality improvement care bundles (Section 2.4). The chapter focuses on AMS globally and in SA (Section 2.5). The chapter concludes with highlights of IS theories and concepts that are the foundation of this research, aiming to fill gaps surrounding CDI care in low resource settings (Section 2.6).

Note that the recommendation to change the classification of *Clostridium difficile* to *Clostridioides difficile* was purposed in 2015, published in 2016, and later accepted by the Clinical Laboratory and Standards Institute in 2018.[1,2] Today *C. difficile* is now accepted by microbial and infectious diseases organisations, as well the published literature. Meanwhile, both *Clostridium difficile* and *Clostridioides difficile* are still used in practice.

2.1 CDI burden of disease: Global to local review

This global to local literature review, first examines CDI with global lens, highlighting the emergence of the infection, outbreaks and occurrence of CDI in the community (Section 2.1.1). The results from high resource settings are relevant because they provide the background for how the results of this thesis provides clarity and novel contributions. Second, this review includes CDI studies including populations with HIV (Section 2.1.2). The limited prior research with CDI findings from patients with HIV is relevant to this thesis set in SA because SA has the greatest number of people living with HIV in the world.[38] Next, this section details limited CDI research in low resource settings and sub-Saharan Africa published before and after commencing on this thesis research, including a recent global systematic review of CDI in low resource settings and notable studies conducted in sub-Saharan Africa (Section 2.1.3). Then, this section focuses on the few CDI studies published in SA.

2.2 Brief global history of *C. difficile*

This section summarizes historical to current key CDI events and findings globally. While *C. difficile* was identified in 1935 and later described as an intestinal colonising bacterium with toxigenic properties, it was not recognized as a pathogenic cause of antibiotic-associated diarrhoea and pseudomembranous colitis until 1978.[53,54] Later in 1978 it was found that vancomycin could treat CDI associated life-threatening pseudomembranous colitis.[55]

Key risk factors for CDI emerged in early studies and remain relevant today. Antimicrobial exposure remains the most relevant risk factor for CDI. Advanced age and healthcare exposure are often confirmed as key risk factors.[4,56,57] A United Kingdom (UK) cohort conducted from 2002 to 2008 found risk of CDI-associated mortality increases with age, from 3.4% in those less than 40 years and up to 41% in those greater than 90 years.[58]

CDI incidence increased in the 1990s and throughout the 2000s. During this time the United States (US) CDC reported a 26% increase in CDI from 2000 to 2001 alone. Also during this time otherwise healthy individuals in the community, thought to be at low CDI risk, developed severe CDI.[59] From 1999 to 2004, *C. difficile*-related mortality increased from 5.7 deaths per million population to 23.7 million deaths per million population.[60] At one hospital in the UK severely affected by two *C. difficile* outbreaks, over 334 CDI cases and 38 *C. difficile* associated deaths occurred between 2003 to 2005.[61]

Globally, many of the catastrophic outbreaks were attributed to a hypervirulent *C. difficile* strain, ribotype 027, known as *C. difficile* BI/NAP1/027.[20] The epidemic strain produced higher levels of toxins A and B, was more resistant to fluoroquinolone antibiotics, and resulted in more severe infection.[15,62] By the mid-2000s, *C. difficile* BI/NAP1/027 was described in hospitals across Europe, including 75 hospitals in England, 16 hospitals in the Netherlands, two facilities in Belgium, and nine facilities in France. Along with reporting the spread of CDI and a potential cost of CDAD to be € 3 000 million/year across Europe, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for *C. difficile* recommended the development of early-warning and response capabilities for *C. difficile*.[12] A global review of CDI and associated mortality reviewed literature between 2005 to 2011 and found attributable mortality varied from 5.7% to 6.9% and all-cause mortality varied from 9% to 38%. Most of the studies identified were conducted in Europe and North America, primarily the UK, Canada and US. The authors concluded studies beyond these settings were needed.[63]

Following these devastating outbreaks, the European Centre for Disease Prevention and Control supported a surveillance study and capacity building across Europe. The surveillance study created a network of 106 laboratories in 34 European countries. The study found 65 different *C. difficile* ribotypes, and the ribotype 027 accounted for 5% of cases. These results led to the conclusion that many other ribotypes were prevalent across Europe.[64]

CDI outbreaks are associated with significant economic consequences due to lengthy hospitalisations and closure of hospital beds/units, increased surveillance, and infection prevention and control activities. For example, the financial burden of *C. difficile* ribotype 027 over one year, affecting 72 patients from May 2013 to 2014, at a tertiary medical centre was estimated to be € 1,222,376. The authors concluded this expense justified heightened awareness and infection and prevention and control (IPC) measures.[14]

Several systematic reviews of CDI and CDI-associated mortality were published in the 2010s. A meta-analysis of hospital CDI-associated mortality compiling 12 studies (8 509 cases and 247,285 controls) for a pooled analysis found CDI patients have a higher risk of thirty-day mortality compared to controls (Odds Ratio [OR] 1.899, 95% CI 1.269-2.840).[6] Another systematic review including 68 studies identified risk factors for complicated CDI are older age, leukocytosis, renal failure and comorbidities. Risk factors for mortality from CDI include age, comorbidities, hypoalbuminemia, leukocytosis, acute renal failure and infection with ribotype 027.[65]

Since the early 2000s, CDI continued to increase in prevalence. However, recent measures to control CDI and antibiotic overprescribing have suggested some improvements in healthcare-associated CDI.[66,67] A recently published large-scale multicentre cohort study of CDI over 2013 to 2017 within a regional network of 43 community hospitals in the US included 2,189,306 admissions. The study by Turner et al.,[17] found a decrease in healthcare associated CDI, while there was no change in community-acquired CDI, showing that the proportion of community-acquired CDI was increasing. The study accounted for changes in *C. difficile* testing protocols and techniques, specifically the change from toxin assay to the more sensitive PCR test, a type of nucleic acid amplification test. The ribotype 027 strain appeared to be controlled over time and geographically and represented a minority of cases. However, the results were limited by variations in definitions of hospital-acquired versus community-associated CDI. The study only recognized healthcare

prior exposure at the facility where the CDI test was performed and missed prior exposure at other facilities.[17] Also, public reporting and financial ramifications to reporting healthcare associated CDI in the US may be creating a bias towards classifying community-associated CDI. Since 2015 the Hospital-Acquired Condition Reduction Program subjected hospitals in the lowest performing quartiles of CDI indicators to receive less payment from reimbursement agencies.[68] Therefore, the change observed by Turner et al.[17] at the community hospitals may be from an actual increase in community associated-CDI, changes in testing practices unaccounted for by the study, or a combination of factors.

A sudden increase in community-associated CDI occurred in the early 2000s.[69] Severe community-associated CDI cases emerged in patients with minimal to no prior healthcare exposure.[70] Recently, a retrospective cohort study published in 2020 from Canada[71] matched 22,617 CDI cases from 2005 to 2015 to controls. The study found a third of cases emerged in the community and long-term care facilities. Compared to patients with similar demographics and medical history, CDI patients had poorer outcomes, longer hospitalisations and rehospitalisations. Globally, hospital- and community-acquired CDIs remain a pressing concern.

An interprofessional team is essential for addressing CDI. The candidate co-authored a review of current epidemics including CDI and described how pharmacists play a key role at points of identifying, treating, and preventing CDI. For example, pharmacists have a growing role to ensure optimized use of antibiotics to reduce risk of CDI. Further, pharmacists might have an increased role in preventing CDI if a CDI vaccine becomes available.[66] The vaccines in development are described by the candidate and co-authors in a review published in the Journal of the American Pharmacists Association.[72] Appendix A presents a copy of this article. Since this review was published, two of the vaccines completed Phase III clinical trials and failed to reach their primary endpoint of preventing CDI.[73,74] However, the Pfizer vaccine trial showed promising results for reducing the duration and severity of CDI episodes.[73]

Today CDI remains associated with severe infection, hospital outbreaks and mortality. Surveillance and infection control measures continue to be high priorities for high resource settings. However, the urgency surrounding this infection in low resource settings is not well described.

2.3 Global review of early CDI and HIV literature

This literature review now dives into the limited studies on CDI in populations with HIV, early studies prior to the deadly outbreaks of the 2000s and more recent findings. While most of CDI literature is from high resource settings, a few early studies investigated the relationship of HIV and CDI. Acknowledging and reviewing the limited studies on CDI and HIV is a pertinent component of this literature review because of the high HIV prevalence in SA and patient populations using the public health system. Furthermore, the relationship of *C. difficile* and HIV in terms of prevalence, severity and response to therapy is not well studied and includes conflicting evidence. Examples of this early literature is outlined here to provide context to the debate and provide detail on the quality of existing literature.

2.3.1 Early literature on CDI and HIV

Studies in the 1990s investigating the relationship of CDI and HIV were modest in sample size and number of sites.[75,76,77] Following several CDAD cases in 1991 within an AIDS ward at a university hospital in Paris, Hutin et al.[78] conducted a case-control study over one-year and found the incidence of CDAD was not statistically different between HIV (4.1/100 patient admissions) and non-HIV patients (1.5/100 patient admissions). While lower CD4 counts were observed in the CDAD group (34 versus 94; P = 0.26), CD4 count and AIDS diagnosis (100% versus 84%; P = 0.16) were not different compared to the control group.[78] Another cross-sectional study compared three study groups: 31 HIV positive patients with CDAD, 31 randomly selected HIV negative patients with CDAD, and 62 randomly selected HIV positive patients without CDAD. Tumbarrelo et al.[75], concluded CDAD was more common and clinically severe in patients with HIV, but not

associated with CD4 count. Among patients with AIDS, CDAD was not associated with any difference in survival.[75] Another early study compared incidence of enteropathogens between hospitals in the UK and Zambia in patients with AIDS. The study did not find any *C. difficile* in 68 patients admitted for chronic diarrhoea compared to an 11% prevalence in London. The authors attributed the difference to low use of antibiotics for prophylaxis and treatment.[77]

Conflicting with Hutin et al.[78] and Tumbarello et al.[75] CD4 count findings, a retrospective study by Barbut et al.[79] compared 34 HIV positive patients with CDAD and matched HIV positive controls without CDAD from 1991 to 1995. The study found a low CD4 cell count (<50 cells/mm3) was associated with CDAD (OR 5.2, 95% CI 1.4-19.3; p = 0.01).[77] Tumbarello et al.[75] and Barbut et al.[79] concluded that *C. difficile* should be considered in immunocompromised HIV patients with diarrhoea.[75,76] These early studies demonstrated a concern for CDI in HIV patients, especially for patients who were severely immunocompromised or had recently received antibiotics. Yet, data on CDAD and HIV in low resources settings and populations in sub-Saharan Africa with high rates of HIV remained absent for years to come.

A prospective study of 161 admissions to an HIV tertiary hospital ward examined the presence of *C. difficile* and CDAD. The study found prior hospitalisation and antibiotic use, including medications for pneumocystis pneumonia and TB, were more common in patients with CDAD. However, TB history was not a significant risk factor. While most patients had advanced disease (median CD4 count 16 cells/mm^3), no patients experienced CDAD associated mortality. Their rapid testing and treatment as part of the study may have improved outcomes. The authors concluded any HIV patient hospitalised with clinical symptoms of CDAD should be tested for CDI and empirically treated while awaiting results.[77] This study was not robust enough to evaluate the relationship of CDI in populations with HIV and TB. Meanwhile, the urgency to test and empirically treat CDI remains under-described in low resource settings, as well as the relationship between CDI and TB.

2.3.2 CDI and HIV before and after HAART

Globally, one of the most robust studies examining CDI and HIV was a large longitudinal record review across nine US cities designed to examine annual incidences of bacterial diarrhoea before and during the highly active antiretroviral therapy (HAART) era. The study included 44,778 persons with HIV infection (mean follow-up 2.6 years) and found *C. difficile* to be the most common bacterial cause of diarrhoea, accounting for 53.6% of all bacterial agents reported (607 of 1 115 pathogens). Risk for bacterial diarrhoea from any cause and from *C. difficile* increased with HIV severity by clinical and immunologic AIDS criteria. Of patients with clinical AIDS, CDAD incidence (9.59 cases per 1 000 person-years) was double that of other bacterial diarrhoea (5.08 cases per 1 000 person-years).[80]

Over the longitudinal study from 1999 to 2002, a non-significant increase in CDAD incidence was observed.[80] However, there was a decrease in incidence of other types of bacterial diarrhoea (OR 0.3, 95% CI 0.2–0.6). Pulvirenti et al.[77] reported the overall incidence of bacterial diarrhoea in the HIV study population (7.2 cases per 1 000 person-years) was at least 100-fold greater than bacterial diarrhoea rates reported for the general US population. Therefore, Pulvirenti et al.[77] concluded healthcare providers should be suspicious of CDAD in immunocompromised patients. The study showed a benefit of HAART longitudinally across a population, specifically a decrease in bacterial diarrhoea in persons with clinical AIDS corresponding with HAART availability.

It is plausible that the non-significant bump in CDAD in the longitudinal study from 1999 to 2002 was an early indicator of the CDAD outbreaks that affected many health systems at this time. However, the study did not report any ribotyping of the isolates at the centers.[80] While this study reports distinctions on risk of CDAD in the HIV population, the study does not delineate the cause of this risk, such as individual factors or a combination of antibiotic and healthcare exposure, or immunosuppression.

A recent study[81] evaluated CD4-cell count as a risk factor for CDI. The retrospective review of 154 outpatient HIV patients with CDI were matched with non-CDI HIV patients between 2003 to 2010. The study found CDI patients were less likely to be taking antiretroviral therapy at the time of diagnosis and had lower CD4 cell counts. Low CD4 cell count (<50 cells/mm^3) increased the risk of CDI. While antiretroviral therapy increased during the study timeframe CDI incidence remained stable annually.[81] Another retrospective case-control outpatient HIV clinic study found low CD4 count increased CDI risk (<200 cells/mm^3).[82] Nevertheless, in low resource settings many patients remain without HIV treatment and are at high risk for bacterial diarrhoea illnesses, including CDI.

2.4 CDI in low resource settings and sub-Saharan Africa

2.4.1 CDI in low resource settings

Globally, a recent systematic review and meta-analysis was conducted to determine the prevalence and incidence of CDAD in developing countries. Including 85 studies with prevalence data, the meta-analysis found that in patients with diarrhoea, CDI prevalence was 15% (95% CI 13-17%). Prevalence was higher in studies including only nosocomial acquisition compared to studies including community acquired or both (p = 0.0227). There was no difference in CDAD prevalence across four regions: Africa–Middle East, developing Asia, Latin America, and China. An incidence density rate of CDI among patients with diarrhoea was calculated from 17 studies and found the incidence density rate to be 8.5 per 10,000 patient-days (95% CI 5.83-12.46).[10]

The few CDI studies in low resource settings, also known as LMICs, published before 2015 focused on strain characterisation. Building on the strain prevalence studies, a recent multi-centre cross-sectional study[83] published in 2018 looking at *C. difficile* prevalence and strain types among hospitalised (n = 608) and control participants (n = 593) found higher *C. difficile* prevalence in Germany (24.0%) and Indonesia (14.7%), compared to Ghana (4.5%) and Tanzania (6.4%). The authors[83]

noted that moxifloxacin is not commonly used at the two African study sites and the results showed no moxifloxacin resistance at the African sites. This, compared to 65.5% moxifloxacin resistance at the Germany site, suggested the ribotypes mirror antibiotic consumption.[83]

2.4.2 CDI in sub-Saharan Africa

Focusing on Africa, a literature review of *C. difficile* concluded that the impact of CDI in sub-Saharan Africa remains poorly understood. The study looked at results in adults since 1995 at the time of review and found only 10 studies from 1995 to 2015. Only one of these studies, a study conducted in Nigeria, found an association between HIV and *C. difficile*.[11] Recently, a prospective study of 135 patients hospitalised at a university hospital in Zambia with acute or persistent diarrhoea determined *C. difficile* prevalence and toxin expression. The study found 10% prevalence (13 patients) and four patients had toxigenic *C. difficile*. There was no significant association with HIV status and *C. difficile*.[84]

Like SA, Nigeria has a high HIV burden. One of the few studies to evaluate *C. difficile* in sub-Saharan Africa was conducted at two hospitals in Nigeria and included 97 patients with HIV infection. Authors estimated CDI prevalence for inpatients to be 43% and for outpatients to be 14%. The study found an association of toxigenic CDI in outpatients with HIV compared to patients without HIV (P = 0.007). The study authors concluded that guidelines were needed for symptom-triggered CDI testing in high risk populations.[85]

2.4.3 CDI in SA

Early studies in SA characterised testing methods, prevalence of toxin genes, and aimed to define prevalence. The 2008 study by Samie et al.[86] aimed to determine *C. difficile* prevalence by PCR. The study was conducted in the Vhembe District and found prevalence to be 14% with about half of the samples being toxigenic. The study found *C. difficile* was not associated with HIV infection. *C. difficile* was more common among individuals greater than 50 years old. The authors concluded

that PCR was a useful method and that *C. difficile* was an underrecognised infection in the region.[86] A 2010 published letter to the editor described one Pretoria tertiary hospital's use of *C. difficile* surveillance following an increase in positive laboratory results. The hospital increased prevention and control procedures, potentially adverting a more severe outbreak.[87]

Rajabally et al.[21] studied the observance of *C. difficile* at a tertiary hospital in the Western Cape. The study evaluated patients with diarrhoea and identified the incidence of CDAD to be 9.2% (59 of 643 patients evaluated prospectively over 15 months). Significant characteristics of patients testing positive for *C. difficile* were recent antibiotic exposure (within 28 days) and healthcare exposure (prior hospitalisation within 90 days). Two patients had the hypervirulent *C. difficile* ribotype NAP1/027 strain. Only recent antibiotic exposure was an independent predictor of CDAD. Here HIV was not associated with CDAD.[21] This study highlights the presence of *C. difficile* in the Western Cape, while the nature of CDI in district level hospitals is unknown outside of this research. Another study led by Rajabally et al.[88] compared testing methods for C. *difficile* and provided ribotyping data in SA from 32 *C. difficile* isolates. The study found *C. difficile* ribotype 017 strains were the most prevalent (50%, 16 isolates), followed by ribotype 001 (15.6%, five patients). While no ribotype 027 strains were detected, ribotype 017 is capable of causing severe disease.[88,89] The predominance of ribotype 017 is like epidemiology results across Asia where ribotype 017 is endemic.[89] Thus, CDI remains an understudied concern in SA.

2.5 CDI treatment and guidelines

Today. *C. difficile* is the most common infectious cause of antibiotic associated diarrhoea. A global pooled meta-analysis representing 5 496 patients, found *C. difficile* accounted for 20% of all antibiotic associated diarrhoea among hospitalised patients.[90] Antibiotic treatment recommendations for CDI have evolved over time with available evidence. The differences in treatment guidelines are described in this section, underlining key distinctions in the SA guidelines from 2015 and 2019

compared to international guidelines along with contributing evidence. This review of CDI treatment and management is organized into sections on available CDI guidelines in 2015, emerging CDI literature, and guidelines today.

Today well-known risk factors for CDI include advanced age, recent antibiotic use with multiple or high-risk antibiotics, healthcare exposure and immunosuppression. Antibiotic use is the most important modifiable risk factor. Antibiotics disrupt the normal bowel microbiota, allowing *C. difficile* to overgrow. Antibiotics with a high risk for CDI include third/fourth generation cephalosporins, fluoroquinolones, carbapenems and clindamycin. Additional risk factors include proton-pump inhibitor use, chemotherapy, gastrointestinal surgery and manipulating the gastrointestinal tract.[4] This section highlights the presence or absence of immunodeficiency as a risk factor for CDI in the guidelines as there is a high prevalence of HIV in SA.[38]

2.5.1 SA CDI treatment recommendations, 2015 to 2020

The SA DoH has used an essential medicines list (EML) paired with Standard Treatment Guidelines (STGs) since 1996. The STGs serve as a standard for practicing in the public health sector. Each medicine included on the national EML is evaluated for effectiveness and use to treat priority health conditions, and then cost and practice factors are also considered. The evidence-based recommendations are guidelines only and do not replace sound clinical judgement. According to a qualitative study,[91] the process of selecting medicines for the EML is evidence-based. Quality, safety and efficacy is considered before cost. The STGs align with the EML as much as possible.[92]

The 2015 SA STGs were in place while this research was designed and conducted. The STGs included brief guidelines for antibiotic-associated diarrhoea. Antibiotic-associated diarrhoea was defined with a mention that CDI may result in severe disease. Diagnosis was confirmed with a positive laboratory result from a stool sample. The 2015 STGs did not give a specific definition of diarrhoea. Meanwhile,

the diarrhoea definition of at least three loose stools within 24 hours has become a CDI testing criteria internationally.[93,94] General management measures include discontinuing antibiotics, oral rehydration unless the patient is vomiting or profoundly dehydrated, and surgery for bowel perforation. A warning in the 2015 STGs stated that "Loperamide is contraindicated as it may result in toxic megacolon."[43] The 2015 STGs do not specify how to discontinue antibiotics. However, this clinical decision should consider indication, especially if antibiotics are treating life-threatening conditions.

The 2015 STGs indicated the initial antibiotic treatment for antibiotic-associated diarrhoea was metronidazole if the diarrhoea did not settle after antibiotic withdrawal. The dosage was 400 mg by mouth every eight hours for 10 days. If the patient did not respond to metronidazole after five days, the guidelines indicated vancomycin parental formulation orally 125 mg every six hours and specialist consult. Note that the 2015 STGs did not specify any conditions where vancomycin should be started as a first-line therapy.[43] Unlike the 2010 Infectious Diseases Society of America (IDSA)/ Society for Healthcare Epidemiology of America (SHEA) and the 2014 ESCMID guidelines at the time, CDI treatments were not stratified by severity in the SA STGs.[94-95]

Previously, infection severity played a larger role in indicating if vancomycin or metronidazole should be used as initial CDI therapy in IDSA/SHEA and ESCMID guidelines.[94,95] The antibiotic choice of therapy for CDI was based on the severity of infection if identifiable by laboratory data, white blood cell count and serum creatinine. Metronidazole was indicated for mild-moderate infection and vancomycin was indicated for severe infection. If the infection was of unknown severity, e.g., if laboratory parameters were not available, the CDI was treated as severe.[94] Per the 2014 ESCMID guidelines, patients with immunodeficiency may be considered at increased risk of severe CDI. However, the ESCMID guidelines did not include immunodeficiency as a separate prediction marker due to limited evidence at the time.[95] The 2015 SA STGs did not stratify CDI antibiotic treatments

by severity or include any treatment guidance for patients with immunodeficiency.[43]

2.5.2 Emerging CDI literature supporting changes in CDI guidelines

Recent primary studies have provided additional evidence for use of vancomycin compared to metronidazole for treatment of CDI. A large cohort study of more than 47 000 patients evaluated all-cause thirty-day mortality among patients receiving metronidazole or vancomycin for CDI and found for patients with severe disease, risk of thirty-day in-hospital mortality was reduced with use of vancomycin compared to metronidazole.[96] Furthermore, a Cochrane review[51] of 22 studies (3 215 patients) found vancomycin was superior to metronidazole for the treatment of CDI and achieving a clinical cure. However, the evidence for this recommendation was rated as moderate because most recent trials excluded severely ill patients for testing new antibiotics in development. The Cochrane review recognised the difference between metronidazole and vancomycin was not large and metronidazole remains less expensive.[51] This cost consideration is relevant in low resource settings like SA.

Fidaxomicin is a newer medication approved in 2011 in the US and Europe for CDI treatment. In clinical trials, fidaxomicin has been shown to reduce CDI recurrences compared to vancomycin, while resolving CDI is like vancomycin.[97,98] As a new medication fidaxomicin remains expensive; however, the medication is cost effective in simulations that consider averted mortality and costs of rehospitalisation and/or treatments for recurrent CDI.[99-101] Fidaxomicin is not included on the SA EML.

Finally, faecal microbiota transplantation (FMT), known as stool transplant, has strong evidence for safe and effective treatment of recurring CDI.[102,103] A recent systematic review of observational FMT studies found the percentage of patients with recurrent CDI achieving clinical cure, as defined by each study, ranged from 68% to 100%.[103] A meta-analysis of randomised controlled trials comparing

medical treatment to FMT found response rates to FMT were higher for CDI patients with recurrent CDI. However, outcomes with FMT compared to medical treatment were not statistically different for patients with their first CDI episode. In SA, FMT treatment availability is limited to only a few academic research centres and is reserved for recurrent episodes.[4,104-105] Pharmaceutical biotherapeutic products in development, such as capsules and suspensions with live microorganisms, show promising potential for preventing CDI recurrences. [75, 106-108] Notably, EBX2660 was safe and effective for reducing CDI recurrences in a Phase II clinical trial.[106] Legal frameworks for regulating FMT and microbiota pharmaceutical products remain unclear in SA.[109-111]

2.5.3 CDI guidelines today

IDSA/SHEA made considerable CDI guideline changes since this project commenced. First, the IDSA/SHEA guidelines published in 2018 changed how initial CDI episodes were classified. Second, IDSA/SHEA published a focused update on the CDI guidelines regarding fidaxomicin and bezlotoxumab in 2021.[112]

The 2018 guidelines designated non-severe and severe CDI.[4] In 2018 guidelines (now outdated), vancomycin or fidaxomicin was recommended for non-severe CDI. Metronidazole was only recommended for non-severe CDI if vancomycin and fidaxomicin are not available. For severe initial CDI episodes vancomycin or fidaxomicin was recommended. Metronidazole was not recommended for severe CDI.[4]

The now current 2021 IDSA/SHEA update elevates fidaxomicin as the preferred treatment for initial episodes of CDI. This change was based on the benefits and safety evidence, especially improved sustained response. However, the 2021 IDSA/SHEA guidelines state that "…vancomycin remains an acceptable alternative if fidaxomicin is not available."[112] The 2021 guidelines also recognize the implementation of fidaxomicin as the preferred agent depends on available resources.[112] Per the 2021 IDSA/SHEA update: "alternative non-severe CDI, if

[fidaxomicin and vancomycin] are unavailable: metronidazole, 500 mg 3 times daily by mouth for 10–14 days."[112]

Also in the 2021 update, fidaxomicin is now preferred for recurrent CDI.[112] The guideline's pooled analysis of four randomized controlled clinical trials found fidaxomicin was more effective for sustained clinical response (initial clinical response without recurrence) at four weeks after completing treatment. However, clinical cure rates (no diarrhoea for two consecutive days after completing treatment), mortality and adverse events between fidaxomicin and vancomycin were similar in the pooled analysis.[112]

The 2021 IDSA/SHEA update suggested bezlotoxumab can be used as adjunctive therapy for patients with recurrence within six months and for patients with an initial CDI episode and high risk of recurrence.[112] The higher cost to patients and healthcare systems for the newer medications, fidaxomicin and bezlotoxumab, remains a concern, and the risks and benefits should be considered.[113]

2.5.4 SA STGs today

Results from this thesis research support national SA guideline changes. The most recent 2019 SA STGs released in 2020 add a few specific management measures and CDI criteria. It states that "[patients] with unexplained and new-onset diarrhoea of more than three unformed stools in 24 hours should be tested" for CDI.[92] The guidelines now specify metronidazole for treating mild to moderate CDI and vancomycin for severe CDI defined by laboratory markers white blood cell count (WCC >15 micromol/L) or serum creatine (SrCr > 132 micromol/L). Other severity predictors indicating vancomycin for initial treatment include immunodeficiency, intensive care admission, serious comorbidity, and age greater than 65 years.[92] This thesis' results, the published abstract of early study results and the recommendations provided to the STG Adult Hospital Level Expert Review Committee support the guideline change to use vancomycin as a first line agent for CDI patients with immunodeficiency. Surgical consult referral is recommended for

patients with complicated CDI and patients not improving after five days of medical therapy.[92]

Infection prevention and control measures are essential to prevent a CDI outbreak within hospitals. The spores are not sufficiently killed by alcohol-based hand sanitizers and must be physically removed with hand soap and water. Contact precautions should use gowns and gloves.[15] The new STGs include contact precautions for known or suspected CDI patients that continue for at least 48 hours after diarrhoea has resolved. The new STGs describe hand hygiene for healthcare workers and close contact.[92]

2.5.5 CDI antibiotic pharmacology considerations

CDI antibiotic pharmacology is described here for metronidazole, vancomycin and fidaxomicin. Metronidazole is from the drug class nitroimidazole antimicrobials. Metronidazole is a bactericidal agent. It causes *C. difficile* cell death and affects other anaerobic bacteria and protozoa.[114] Metronidazole crosses the cell wall of both anaerobe and aerobic bacteria, but its bactericidal mechanism targets obligate anaerobe bacteria like *C. difficile*.[114] First, a metronidazole nitro group is reduced in the cell. Then metronidazole's toxic metabolites oxidize deoxyribonucleic acid (DNA) and cause DNA strand breakage in addition to inhibiting protein synthesis.[114-115]

Oral metronidazole has high bioavailability with greater than 90% of the drug absorbed from the small intestine.[115] This high absorption limits the amount of drug directly entering the colon, the site of CDI. After oral administration, metronidazole activity lasts 12 to 24 hours with an average half-life of eight hours.[115] The liver metabolises metronidazole. It is a major substrate of liver enzymes and inhibits liver enzymes (CYP2C9 and CYP3A4), resulting in drug interactions.[116] A dose reduction is recommended for patients with liver disease. Dose adjustments are usually not necessary for kidney disease.[115] Metronidazole and its metabolites are excreted in urine by the kidneys. Only a small portion, about 6% to 15%, is secreted

into the colonic lumen.[117-118] Colonic metronidazole concentration decreases as disease improves, suggesting metronidazole diffuses through colonic lesions. This limitation of metronidazole may be related to higher CDI relapse rates.[119]

Vancomycin is a glycopeptide antibiotic.[120] Its bacteriostatic or bactericidal properties vary by pathogen targeted and drug concentration at the site of infection.[121] Vancomycin is bacteriostatic against *C. difficile*.[122] Vancomycin interferes with gram-positive bacterial cell wall synthesis by binding cell wall precursors.[120] In contrast to metronidazole, vancomycin has poor oral bioavailability; it is not well absorbed from the gastrointestinal tract. High concentrations of vancomycin reach the colon.[123] For systemic infections it must be administrated intravenously; then, it requires added dosing by kidney function and monitoring considerations.[124]

Fidaxomicin is a macrocyclic antibiotic that is bactericidal against *C. difficile* by targeting targets bacterial RNA polymerase.[124] Like vancomycin, fidaxomicin and its active metabolite achieve high stool concentrations with minimal systemic absorption.[125] Thus, there are no hepatic or renal dose adjustments needed and it has a low risk of drug interactions.[126] However, unlike metronidazole and vancomycin, fidaxomicin has additional AMS benefits. Fidaxomicin is a narrow spectrum antibiotic. Fidaxomicin can inhibit *C. difficile* sporulation, an effect not seen with metronidazole and vancomycin. These features might be related to the lower recurrence rates with fidaxomicin that supported the guideline changes described above, now indicating it as a first-line agent for initial non-severe CDI.[127]

2.6 Improving quality in healthcare

Improving healthcare quality is a globally recognized need in high and low resource settings. The World Health Organisation (WHO) recognises the need to improve quality and access to care. Access alone will not ensure achieving universal health coverage goals, a component of the United Nations' Sustainable Development Goals for 2030.[128] A 2018 Lancet Global Health Commission systematic review of

137 countries found that the lack of quality care is a greater barrier to reducing mortality than lack of access. More than eight million deaths per year in LMICs result from poor-quality health systems and could be prevented.[129]

Quality improvement methodology is often applied to the healthcare sector with variable success. Quality indicators can include components of structure, process and outcomes in healthcare. To measure success, clinical indicators are often necessary. Then, these indicators can be used to set targets.[130] Differences in success are linked to differences in context. A combined systematic review and expert panel study found 25 contextual factors that were hypothesised to be associated with quality improvement success. [86,131]

Batalden and Davidoff[132] proposed a simple and highly cited three component formula to improve quality:

$$Generalisable\ scientific\ knowledge + Particular\ context \rightarrow Measured\ improved\ performance$$

Their formula emphasizes that a key component of quality improvement is measuring and characterising the setting's context. Measurements of baseline data are critical to evaluate change.[87] The "+" symbol represents the knowledge need for adapting evidence to a particular context. The "→" symbol represents the knowledge required to drive change change.[132]

Therefore, this thesis' research is critical to any quality improvement initiative for CDI as it provides baseline data on performance and context of low resource settings. Baseline CDI management practices were identified and reported (Objectives 1 to 2 and 4). Context in improving quality includes mapping healthcare processes. The processes of managing CDI are addressed in this thesis with study Objective 2. The context gathered from Objectives 1 to 2 informed the development of the CDI intervention for Objective 3. An analysis of the intervention and the results were then reported (Objectives 3 to 4).

2.7 Care bundle approaches to improve quality

The care bundle approach to improve quality leverages evidence-based practices and links them together to be delivered consistently to improve quality of care.[26] Many successful care bundles have been implemented in intensive care units and for specific conditions such as chronic obstructive pulmonary disease, surgical site infection, *Staphylococcus aureus* bacteraemia as well as preventing CAUTI and CLABSI.[27, 133, 134]

One of the most effective quality improvement initiatives is the revolutionary work on preventing central venous catheter bloodstream infections in Michigan, US, that has now been sustained for 10 years.[135] After its initial success, Dixon-Woods et al.[136] created an updated project theory and found the project's success was attributable to "using several interventions that functioned in different ways to shape a culture of commitment to doing better in practice."[92] This theory reflects the bundle approach of the intervention.

A systematic review and meta-analysis compared care bundles to standard of care to evaluate the risk of negative patient outcomes. The study found bundles might improve care, but the evidence quality was low due to bias and inconsistencies. Bias was observed in the results in that non-randomized 'before-after' studies were likelier to report positive findings, while evidence from randomized bundle implementation trials was uncertain. The authors found that better reporting of implementation strategies, such as mechanisms of action for delivering the intervention, is needed in future studies.[27]

A separate review of acute care bundles reviewed 99 quantitative publications from 2001 to November 2017 (106 care bundles) and classified implementation strategies with the ERIC framework. The review included implementation compliance and care bundle elements. Only one study included was specific to CDI. The analysis of the studies found the following factors improved compliance: evaluative and iterative approaches, developing stakeholder relationships, and education and training strategies. Care bundles with fewer elements and bundles that met criteria for being simple were associated with better compliance.[91,137]

A systematic review of IPC promotion strategies for nurses in sub-Saharan Africa was conducted and included publications from 1998 to 2018.[138] The study concluded better IS-specific research is required to understand which implementation strategies should be used to promote IPC. The review study did not identify or include any IPC bundle approaches specific to CDI, while other specific disease states were included in the study attributes table. Nevertheless, the review results are relevant to this thesis because nurses play a key role in CDI IPC practices, especially hand hygiene and contact precautions.

2.7.1 CDI care bundles

A limited number of CDI care bundle and intervention studies have been published in high resource settings.[9] Many of these studies focus on IPC. For example, a simulation model of CDI incidence found a bundle approach of CDI interventions could reduce *C. difficile* acquisition and infection rates with the most impactful interventions related to IPC and empiric treatment of suspected cases.[139] An early checklist approach to a CDI care bundle proved to be effective and reduced CDI incidence by 40% after the intervention implemention.[140]

A systematic review of CDI prevention bundles published in 2017 included 26 studies.[9] The review assessed bundle components, implementation components and adherence to the bundle. All studies included reported positive improvements in CDI. However, the studies were limited by variable implementation and adherence factors. Thus, the studies were incapable of proving a causal relationship between the bundle and outcomes due to poor research rigor. The authors concluded cluster randomised CDI bundle intervention studies are urgently needed.

2.8 Antimicrobial resistance and AMS

CDI, antimicrobial resistance and AMS are related. *C. difficile* is an antibiotic resistant pathogen and overgrows in the presence of most antibiotics.[29] Antibiotic

overuse accelerates antimicrobial resistance threatening modern medicine and increasing CDI risk.[30-32] Furthermore, use of high-risk antibiotics independently increases the risk of CDI.[32] Thus, AMS is vital to reduce the development of antimicrobial resistance across all pathogens.[141] CDI rates can be an indicator of successful stewardship programmes.[142,143] Thus, this section provides background on antimicrobial resistance and AMS, and their intersection with CDI.

2.8.1 Antimicrobial resistance

Antimicrobial resistance is a global threat.[144-146] Antimicrobial resistance threatens our ability to treat routine infections and provide medically necessary surgeries if effective antibiotics are not available. Since the early clinical use of penicillin in the 1940s, antibiotics have revolutionised medicine, but now antibiotic resistance is outpacing the development of novel antibiotics. The slowed development is in part due to a lack of economic incentives.[30] A UK economic report estimated the global burden of antimicrobial resistance and outlined intervention steps.[147] Per the final report published in 2016, antimicrobial resistance is expected to attribute 10 million deaths per year by 2050 globally and cost the global economy USD 100 trillion without multifaceted interventions.[147] A 2022 analysis of the clinical pipeline reported there are now 76 new antibiotics in development and clinical trials, including 15 novel agents targeting *C. difficile*. However, few are close to reaching the approval stage.[148]

Antimicrobial resistance is complex in low resource settings. A systematic review found more than 40% of African countries do not have data on antimicrobial resistance and from the limited available data there is resistance to commonly prescribed antibiotics.[149] A global study found a negative association between gross national income and prevalence of antibiotic resistance in invasive samples, showing an urgency for antimicrobial resistance policies in low resource settings.[150] Factors attributing to antimicrobial resistance in developing countries were described through a systematic review and identified the following:

- A lack of surveillance of resistance development,
- Poor quality of available antibiotics,

- Clinical misuse, and
- Ease of availability of antibiotics.[151]

A 2019 report update concluded not enough progress has been made on the 2016 recommendations.[152] One of the areas lacking progress relevant to this thesis is compliance with IPC as a means of limiting the spread of multidrug resistant (MDR) pathogens. IPC compliance remains a challenge in high and low resource settings and the quality of IPC studies is limited. Globally, understaffed and overcrowded healthcare systems contribute to reduced IPC compliance and is especially challenging in low resource settings.[152] Therefore, the themes surrounding IPC in low resource settings investigated within this thesis contribute to the global conversation on antimicrobial resistance.

2.8.2 AMS and CDI

While multisectoral approaches have been organised to combat antimicrobial resistance, antibiotics must be used appropriately to limit the development of antimicrobial resistance and improve patient outcomes. The WHO recognises AMS programs aiming to optimise antimicrobial use as a key strategy against antimicrobial resistance with the WHO's Global Action Plan.[144,145]

The primary goal of AMS was described in the 2007 IDSA stewardship guidelines [50]: "to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *C. difficile*), and the emergence of resistance". Antimicrobial stewardship programmes (ASPs) can include a variety of interventions such as a prospective audit with feedback, formulary restrictions and preauthorisation. A systematic review and meta-analysis of hospital-based stewardship programmes found the programmes resulted in decreases in antibiotic consumption and cost. Hospital length of stay and rates of antimicrobial resistant infections improved.[153]

Globally, pharmacists take a leadership role on AMS committees in healthcare systems, especially secondary and tertiary levels, to support appropriate antimicrobial prescribing.[154,155] Roles for pharmacists to practice AMS in primary care and the community are emerging.[154,156] A systematic review of 35 AMS trials involving a pharmacist demonstrated a positive impact on antibiotic prescribing.[157] The analysis included studies from the US, UK, Australia, Europe and Asia. In SA, a prospective pharmacist driven stewardship programme resulted in improvements in antibiotic prescribing across 47 private sector hospitals.[158] The study results are not directly transferable to the public sector where resources are substantially different, especially a lack of electronic medication ordering. Today, AMS recognises the need for all healthcare professionals to be stewards of appropriate antibiotic use.[159]

Governments, hospitals and professional societies around the world are working on developing education for healthcare workers on antimicrobial resistance and AMS. Programs include courses, workshops, conferences, guidelines, public outreach materials and online-resource websites. Notably, a global review of these programs identified 94 programmes, including two educational programs in Africa that are based in SA.[160] The University of the Western Cape (UWC) has a course in rational use of medicines that is available to healthcare providers.[160] The SA Antibiotic Stewardship Programme has an online course for medical students and physicians.[160]

AMS is critical in preventing CDI. Antibiotics increase CDI risk, and that risk is increased by all elements of antibiotic use, such as duration and the use of multiple antibiotics. CDI risk is highest during antibiotic use and in the 90 days following antibiotic use.[161,162] Thus, ASPs that improve appropriate antibiotic prescribing can have a positive impact on CDI, and AMS bundles have been associated with reduced CDI incidence.[163,164]

Multiple systematic reviews have shown the positive impact of AMS on antibiotic prescribing and patient outcomes.[165-167] While most AMS studies have been

conducted in high resource settings, a systematic review was recently conducted with a focus on LMICs.[168] After screening more than 2 000 articles, the study identified 27 studies from LMICs representing two low-income and 11 middle-income countries. The systematic review included studies that were interrupted time-series, randomised and non-randomised controlled trials and excluded studies without a control. The review concluded that the studies showed positive effects but were subject to medium or high levels of bias.

In SA, addressing AMS is a national priority and this thesis aligns with the SA National Antimicrobial Resistance Strategy.[28] A systematic scoping review of stewardship interventions in SA public and private sectors was conducted for a timeframe of 2000 to 2019. The review identified 18 studies and categorised interventions in broad categories (prescription audits and usage; education and its impact; and other AMS interventions) and the role of different healthcare professionals. The review emphasises the national commitment from private and public sector health systems to address antimicrobial resistance. However, most of the studies selected were from one private sector hospital network and the limited stewardship work in the public sector was primarily conducted at tertiary hospitals. The study acknowledges that many settings remain understudied with scarcities of antimicrobial resistance and stewardship data.[169] Therefore, vast gaps remain in understanding antimicrobial resistance and stewardship in the context of public district level hospitals in SA.

In the Western Cape public sector, one of the two tertiary hospitals has a developed ASP. This is the hospital where Rajabally et al.[21] conducted the initial CDI research. They credited the stewardship programme as a possible explanation for the lower observed rate of CDAD compared to western countries. However, the ASPs were less developed or non-existent at the district level hospitals where this thesis' research was conducted. Today, the Western Cape Department of Health and Wellness supports expansion of an antibiotic stewardship programme that is being incrementally implemented across facilities.[170]

2.9 Conceptual framework

2.9.1 IS and quality improvement

IS is gaining recognition for health system change, in part, because its frameworks often encapsulate well-grounded conceptual theories.[171] The National Institute of Health Fogarty International Centre[40] defines IS as the "study of methods to promote the integration of research findings and evidence into healthcare policy and practice". IS encourages describing interventions in enough detail, including specific steps taken and by whom, so that others can reproduce it.[172] A goal of the field is to reduce the lag time between research findings translating into evidence-based practice.

While quality improvement intersects with IS, the two concepts are not inclusive of each other. IS can support effective quality improvement and be applied to fields beyond healthcare. Likewise, improving quality can occur without recognising IS principles. In other words, IS provides a common language, theories and frameworks to improve the science. IS researchers Haines et al.[173] clarify that IS can include methods and strategies for improving practice by optimising fit among evidence-based practices and the contexts in which they are implemented. Nilsen[174] explains the numerous IS theoretical approaches as addressing three overarching aims: "describing and/or guiding the process of translating research into practice (process models); understanding and/or explaining what influences implementation outcomes (determinant frameworks, classic theories, implementation theories); and evaluating implementation (evaluation frameworks)."

Context is cited as a determinate for achieving change with quality improvement, and context is a term that occurs in numerous IS frameworks, directly defined as individual constructs and indirectly with similar terms, and in various aggregation levels.[175,176] A scoping review of IS found the most common dimensions of context to be organisational support, financial resources, social relations and support, leadership, and organisational readiness for change.[176] One IS framework that

excels in identifying contextual factors surrounding an intervention, that may otherwise be missed, is the CFIR.[47]

2.9.2 CFIR

The CFIR is a widely used meta-theoretical IS framework. It incorporates published implementation theories and frameworks to provide a pragmatic structure to IS with five major domains:

1. Intervention characteristics,
2. Outer setting,
3. Inner setting,
4. Characteristics of individuals involved, and
5. Process of implementation.[47]

Within the CFIR there are 39 theoretical constructs listed across the five domains. The CFIR constructs include aspects of generalised theory, such as Rogers' Diffusion of Innovation landmark theory[177] and constructs published by Greenhalgh et al.'s [178] systematic review of diffusion of innovation in service organisations (e.g. tension for change, readiness for implementation, opinion leaders).[47,178] Eighteen additional state-of-the-science models were analysed to create the CFIR.[47] Elements of the socioecological framework are observed in CFIR: community and organisation.[179]

As a determinant implementation framework, CFIR describes context as covering a "broad scope of circumstances and characteristics" and states that "[context] consists of a constellation of active intervening variables and is not just a backdrop for implementation".[47,180] Furthermore, the CFIR provides "an overarching typology to promote implementation theory development and verification about what works where and why across multiple contexts".[47] By using well-developed theory within IS frameworks when evaluating the implementations of evidence-based interventions, usable and generalisable knowledge can emerge.

The CFIR has been cited over 5 000 times, according to iCite, since published by Damschroder et al.[180-183] in 2009, including a few analyses of interventions in low resource settings, with several conducted in Kenya and Mozambique. In SA, a few CFIR applications have been used to evaluate preventing mother-to-child HIV transmission protocol implementation.[184] Beyond this work, IS research with CFIR in Africa is limited.

The CFIR was selected for its strengths in adaptability and components that apply to this study. The CFIR strengths compared to other models of dissemination and implementation have been outlined by reviews in the literature and informed the selection of the CFIR for this study. Another strength of the CFIR is that it supports implementation and the integration of evidence-based interventions within a setting.[179] The CFIR combines multiple determinant frameworks.[174] Subsequently, CFIR, like other determinate frameworks, includes constructs that act as barriers and enablers to implementation.[174]

Theories enhance our understanding of relationships, change mechanisms and can predict outcomes. The CFIR incorporates theories from multiple fields and originates in health services research.[179] This study will use the CFIR meta-theoretical framework to examine the intervention. Specifically, the CFIR will frame and identify factors influencing the implementation successes or failures within this study.

2.9.3 ERIC

Also as part of our methods, this study follows guidelines for naming, defining and operationalising early implementation strategies with consistent language from the ERIC strategies outlined in IS by Powell et al.[42] Developing relationships with diverse partners is a principle to IS and this study used ERIC terminology to describe early engagement with key partners.

2.10 Literature review summary

Care bundles are a promising intervention for improving quality. However, much of the care bundle research has been conducted in high resource settings, and in this setting the programmes often lack research rigor. While CDI-specific bundle interventions have proved to be effective interventions, CDI research lags in low resource settings compared to other disease states. The literature review included in this section showed how better-quality implementation research around care bundle interventions is needed globally, in high and low resource settings. This literature review identified components of implementation research that were necessary for success, especially in understanding the context.

Thus, this thesis provides crucial first steps for CDI quality of care improvement in low resource settings by providing context on quantitative and qualitative CDI factors, as well as factors influencing intervention uptake. Specifically, this thesis addresses debates in the field on the relationship between CDI and population-specific risk factors, such as HIV. The first results chapter on epidemiology and outcomes provides baseline measurable statistics on CDI quality of care and patient outcomes. The second results chapter provides qualitative context on CDI workflow, facilitators, and barriers to care. The third results chapter provides a context informed CDI intervention and identifies CFIR constructs associated with uptake.

Then, the results could inform innovative context-specific solutions that could be scaled at a system level and adapted to unique environments, especially because this research used well-documented quality improvement principles and theory-based IS approaches throughout.

3 METHODOLOGY

This chapter describes the research's methodological approach. The chapter begins with stating the candidate's positionality (Section 3.1). The overall research design and research setting are presented (Sections 3.2 and 3.3). The chapter includes a summary of the IS strategies used to develop the research study. Data collection and analysis methods are detailed (Section 3.4). The rationale for the methodology choices underpins this chapter. This chapter provides additional detail on the methodology, especially the research design and research setting, which was beyond the scope and word count limitations of each publication. Inevitably, some key components of the methodology, approaches and data analysis are included in this chapter and publications. Ethical considerations and approval details from the UWC and the SA's DoH are included at the end of this chapter (Section 3.5), along with research funding information (Section 3.6).

3.1 Positionality, reflexivity and rigour

I, Laurel Legenza, am a PhD doctoral candidate in the Faculty of Natural Sciences, School of Pharmacy at the UWC, SA. Currently, I am a pharmacist researcher. I also lead AMS research in the US, at the University of Wisconsin (UW)-Madison, School of Pharmacy. Where at the time of writing this positionality statement, I was a post-PharmD postdoctoral fellow. Also, I teach global health courses and lead our School of Pharmacy, Office of Global Health as a Teaching Faculty associate.

My research focus is on improving patient outcomes, specifically addressing antimicrobial resistance with action-oriented information. The CDI checklist provides evidence-based CDI treatments with a context-informed implementation package. In Wisconsin, I am developing tools to support antibiotic resistance decisions that incorporate the local antimicrobial resistance patterns. My long-term goal is to curb antimicrobial resistance and its associated patient morbidity and mortality. I am a pharmacist who believes that the discipline of pharmacy can

positively impact patient care at the point of care and with collaborative systems-level interventions. As part of this PhD thesis, I applied principles from quality improvement and IS with the aim of health systems strengthening. My positionality and experiences influence my research. As such my identity is described here with transparency, along with pieces from my journey becoming a pharmacist researcher. I reflect on my decisions during the research process and how they shape this thesis.

I am a white, cis-gender woman, from a mostly white, northcentral Wisconsin town, in the US. My pronouns are she, her and hers. I am a first-generation college graduate and the first of my family to be a PhD candidate. I am privileged to be the first fellow for the inaugural Comparative Health Systems Global Pharmacy Fellowship at the UW-Madison, School of Pharmacy. The fellowship provided funding for me to complete this thesis research in SA.

My worldview has evolved since beginning this CDI research in SA. Notably, a substantial portion of this thesis was written from the safety of my home during the initial phases of the Covid-19 pandemic and shelter-in-place orders. Through my window, the sounds of 2020 racial justice protests organising at the park and marches to the Wisconsin state capital infused this thesis with greater purpose towards health equity in SA and beyond.

I believe decolonisation requires collaborative global efforts between those with resources who have benefited from colonisation and historically colonised populations. I carry my white identity and privilege with me in my global health work and believe those with privileges should do the work to address health equity, but the prioritisation of problems and solutions must come from those in need. This was our research team's approach in listening to the local healthcare providers and stakeholders to identify CDI as the topic area of this research. Then, we submitted our research protocol for ethical approval at the Humanities and Social Science Research Ethics Committee, Department of Research Development of the University of the Western Cap, before obtaining additional approvals. This process

helped protect research participants and ensure the research followed ethical standards. I hope that our global health research results in mutually beneficial bi-directional experiences and health systems strengthening.

As part of my early undergraduate studies, like many pre-health professional students, I wanted to study health sciences and help people. I maintained interests in cultures, language and arts which led to earning my double major in Biology and Spanish, including a six-month semester abroad in Spain. Five years later, I was able to complete part of my PharmD experiential training via a clinical rotation in at La Paz University Hospital, a tertiary medical centre in Madrid, Spain. Through studying abroad my worldview expanded, and I gained skills in humility and communication across cultures that I believe helped prepare me for my PhD research in SA.

My clinical PharmD training in the US centred on evidence-based pharmaceutical care but included aspects of healthcare systems, medication safety and quality in healthcare. My interests in health systems and leadership led me to deepen this knowledge base with my Master's in Health-System Pharmacy Administration at the University of Utah. Through my master's, I learned from some of the leading health system pharmacy researchers and administrators. I learned how a health system pharmacy department deploys advanced technologies to provide safe and effective medications with exceptional accuracy. Also, I learned how a large staff of pharmacists provide advanced clinical pharmacy services in each area of the hospital, working with interprofessional healthcare teams, reviewing every medication, and making patient-centred evidence-based medication recommendations to the healthcare team. However, most of the world's hospitals do not operate with clinical pharmacists placed throughout the hospital. Simultaneously, the US healthcare system is the most expensive, by proportion of gross domestic product in the world. The US, rich with resources: staff, technology, and tools, ranks last in many health outcomes among other high-income countries.[185] Opportunity to improve the quality of care exists across settings. Thus, my research embodies questions such as:

- What can low resource and high resource settings learn from each other to improve health outcomes?
- How can we do more with less to improve healthcare outcomes?

The context-informed CDI intervention brought together evidence-based medicine and IS with the goal of improving the quality of care provided. I chose to use CFIR as the theoretical framework for analysing the intervention because it efficiently incorporates many established theories into one adaptable and comprehensive framework.

During my master's, I learned about methods for rigor in research and research ethics. I designed data collection, collaborated with pharmacists and engineers, and led data analysis for the project measuring workload before and after implementing a centralized call centre for outpatient pharmacies. The results were published in the *American Journal of Health-System Pharmacy*.[186] The rigor of my PhD research builds on my early training in quantitative research and adds rigorous methods in qualitative research. Qualitative interviews were transcribed verbatim and coded with qualitative software by two additional researchers. This helped in reducing my own bias. The third publication included three SA physician collaborators as co-authors who together helped limit bias by providing the local healthcare provider voice and critical review of the results.

The mixed methods research conducted during my PhD required agility in responding to the results in real-time data collection. First, during quantitative data collection, via the retrospective chart review, we realised that calculating rates of recurrence was not feasible. The available documentation did not clearly state if the CDI was the patient's first or subsequent episode. The physical thickness of the medical charts provided varied. Patients sometimes had multiple folders for each hospitalisation, while other folders included many past hospitalisations in one folder. It was unclear if all the relevant information included was for past visits and hospitalisations. Then, we realised the magnitude of a more devasting outcome associated with CDI that was measurable, in-hospital mortality. I remember

reviewing the paper medical records at the hospital during data collection. Every fourth folder from a patient with CDI had a slash across the front with a red marker indicating that the patient was deceased. Our research responded by focusing on in-hospital mortality and the significant survival differences between patients with positive and negative CDI test results.

The second major instance of responsiveness occurred during the interviews with healthcare providers about CDI. I acknowledge that my identity may have influenced the way interviewees responded to my request for an interview and the interview questions. I appreciate the participants' time and honest responses. Their level of comfort in the interview and with me seemed to increase as the interview went on. One interviewee is quoted stating: "It's actually the first time that I hear about [CDI], to be honest."[187] In response, the semi-structured interview guide was adapted during the interviews to broadly inquire about care for patients with any type of diarrhoea, not just CDI-specific questions. Later, we developed a scoring system to measure and document the wide range of CDI knowledge among healthcare providers. From the qualitative interview results, we mapped the workflow steps for CDI care at district hospitals, barriers and facilitators.

For me, a career in research is a continuation of my persistence to weave together my passions for art and science. For example, with this PhD research, we put together existing knowledge and literature to address the gaps in CDI care in SA. This required developing creative solutions within the local context and resources and then communicating them effectively. We reported our findings to the healthcare providers and administrators at the DoH and published the results in accredited open-access international journals. We wanted to make sure anyone who was interested in this research's results could find and access it.

Throughout my training, I am grateful to my extraordinary mentors who have influenced my worldview, research style and science communication. In turn, I appreciate opportunities to teach and mentor. As part of this PhD research, I have led local and international teams of students involved in the research process. At

the time of writing this statement, I teach an online global health course, the first course in the series for the Global Health Certificate for graduate students and professionals at the UW-Madison. I advise pharmacy students interested in global health at the UW-Madison School of Pharmacy.

Today, I am an active member of the International Pharmaceutical Federation (FIP), a global organisation representing over four million pharmacists and pharmaceutical scientists. I serve as the Secretary for the World Hospital Pharmacy Research Consortium, a part of the FIP Hospital Pharmacy Section (HPS) where I facilitate international research collaborations. I was awarded a 2022 FIP HPS grant for my proposal 'A pharmacy-led train-the-trainer intervention program for CDI in public hospitals'. The award will support extending this PhD CDI project in SA with my supervisor, Dr Coeztee, and pharmacy clinical master's students leading CDI training in public hospitals.

3.2 Research design

Overall, the research follows a mixed methods approach leveraging qualitative descriptive and quantitative research methods, as well as the meta-theoretical CFIR Framework. This study has multiple inductive and deductive components.

First, we take an inductive approach to understand CDI and map the barriers and facilitators to CDI care. For the epidemiology study, we do not test a hypothesis and were unable to calculate recurrence. However, the data itself directed us toward examining mortality and risk factors for CDI. For the qualitative study, we do not base the research approach on an existing theory or specific framework, but we map workflow as derived from the rich data collected. In this pragmatic approach, the thesis contributes to the body of knowledge a framework/theory for the barriers and facilitators to CDI care within the derived real-world workflow for identifying, treating and preventing CDI.

Next, the quantitative and qualitative results informed the development of a CDI intervention.

Third, in the third results chapter, we conduct a secondary deductive analysis, we apply CFIR to the entire study design from identifying the problem to developing an intervention. This third analysis identifies the relevant theory-based constructs associated with the intervention's development, implementation process, and use among the three participating hospitals.

3.2.1 Applied theory and frameworks

Early in the development of this research study, we, the candidate and research team, developed stakeholder interrelationships and designed the quantitative and qualitative research studies to serve as baseline evaluative information to inform and measure future quality improvement interventions. This approach aligns with IS and quality improvement principles.

Table 1 describes the specific ERIC implementation strategies used and pre-intervention actions taken. This table provides detail of actions taken to identify the topic area and build relationships within the Western Cape and SA DoH. Additional ERIC strategies specific to the intervention and implementation are a part of the results in the Chapter 6 publication methods section.

This study provided context regarding the care of patients with CDI in public district hospitals with quantitative and qualitative data. Constructs related to context are included within the CFIR components of the outer setting and inner settings. Components of CFIR's inner setting (tension for change, available resources and learning climate) were addressed within the analysis of qualitative data (Objective 2).

Next, results generated from this thesis research will inform the development and implementation of CDI quality improvement interventions in the 'real world',

specifically in the resource constrained environment of urban public sector hospitals in Cape Town, SA. This study's results were used to describe the relationship between interventions and impact on outcome measures included in study Objective 1.

Finally, the intervention, implementation and results were analysed with the CFIR conceptual framework to report study findings and inform future interventions (Objective 3). CFIR was chosen as the theoretical framework because it is a meta-theoretical framework and draws on multiple evidence-based theories contributing to IS. A strength of the CFIR framework is that it is adaptable to local context and can identify constructs associated with intervention uptake.[47] The CFIR analysis identified theoretical constructs associated with the uptake of the CDI intervention. These strengths made CFIR a practical and efficient choice for our real-world research.

Therefore, this project uses the existing language in the field of IS. The research aims to use implementation strategies and frameworks to produce a quality improvement intervention that may be transferable, replicable, and/or scalable to other healthcare settings. This study can advance the field of IS by providing empirical evidence for the CFIR framework.

3.2.2 Selection of research area: CDI

CDI was chosen as the research area through a local needs assessment of healthcare providers, stakeholders and infectious disease leaders. The research area was selected by internal SA leaders and healthcare providers through the following two phases. First, the topic area of AMS was selected as the candidate's research area, through visits with stakeholders, including DoH administrators. Second, the candidate led a strengths, weaknesses, opportunities and threats or SWOT analysis of AMS projects and innovation areas, and CDI was selected as the specific project due to the scarcity of available data on CDI at the district level in the Western Cape province.

Table 1. ERIC implementation strategies used to develop foundation for quality improvement research

ERIC Strategy[a]	Actions taken
Develop stakeholder interrelationships	
Conduct local consensus discussions and needs assessments	• Conducted a country-wide needs inventory of the SA healthcare system at administrative, operational, supervisory, managerial and patient care levels to identify the research and future intervention topic. • Consulted with academic leaders at various universities across SA and in Cape Town. • Narrowed needs inventory to the Western Cape province level. • Consulted with stakeholders at policy level regarding needs in public and private sectors (e.g., pharmacy services, Western Cape Department of Health and Wellness). • Consulted with infectious disease leaders in public and private sectors (e.g., SA DoH, private sector heads of microbiology). • Consulted with internationally-recognised infectious disease researchers and clinicians in SA and the US, including those leading work in AMS and CDI. • Presented chosen problem to leaders previously engaged in needs assessment and departments of internal medicine to affirm chosen problem was important and determine if planned clinical innovation to address it was appropriate.
Build a coalition	• High-level hospital chief executive officers and administrators were engaged for research approval.

	• Heads of departments and managers assisted with introductions to the 'educationally influential' and local opinion leaders to recruit and cultivate relationships with partners in research effort.
Develop academic partnerships	• Strengthened existing academic partnership between the University of Wisconsin (UW)-Madison and University of the Western Cape (UWC) Schools of Pharmacy. • Engaged pharmacy students from universities for shared training and skill-building with the research project, including partnership with the one-year UWC longitudinal research program for final year pharmacy students (two groups of students over two years) and inclusion of UW-Madison independent study and Advanced Pharmacy Experiential Education (APPE) students.
Use evaluative and iterative strategies	
Conduct local needs assessment	Conducted baseline CDI management retrospective review.
Assess for readiness and identify barriers and facilitators	Identified barriers and facilitators through qualitative interviews with healthcare providers and stakeholders.
a. Expert Recommendations for Implementing Change (ERIC) strategies (Powell et al. *Implementation Science* 2015)[42]	

The quantitative baseline data were collected via a retrospective medical record review at four secondary hospitals. The data collected objectively described how and when CDI was identified, which patients were experiencing CDI, how patients were treated, and what were the patients' outcomes. Quantitative methods explored and described the epidemiology of CDI in SA. Patient demographics and past medical history data were collected to evaluate CDI risk factors in SA such as recent

antibiotic use, healthcare exposure, age and comorbid conditions. Data on the timeline of CDI lab testing, CDI antibiotic selection and additional patient management criteria and CDI-related infection control precautions. The data variables collected are listed in the CDI Data Collection Form (Appendix B) and detailed in the CDI Data Collection Instructions Manual (Appendix C).

Qualitative data collection included interviews with key informants at the hospitals about current CDI practices and perceptions. A semi-structured interview guide (Appendix D) guided interview. The interview guide was developed with the Systems Engineering Initiative for Patient Safety (SEIPS) model, a framework that describes interactions between work systems (tools/technology, tasks, person, organisation, environment), processes and outcomes.[188] The interview questions were designed to reveal:

1. CDI workflow processes: steps to identify, diagnosis, treat and prevent CDI.
2. Facilitators and barriers to providing CDI care.

Twenty-eight qualitative interview and focus groups were conducted with frontline and administrative healthcare providers including nurses, pharmacists and physicians at the participating hospitals. Semi-structured interviews were conducted in-person at a location convenient for the interviewee, such as in hospital ward offices, administrative offices or the pharmacy. Section 3.4 presents the data collection.

The quantitative and qualitative data, as well as input from local collaborators informed the intervention development and implementation. We planned to develop a quality improvement intervention; the specifics of the intervention were developed on-site in collaboration with local healthcare providers. The intervention checklist included measurable aspects of CDI care that needed improvement and was designed to fit the workflow and resources available elucidated by the qualitative interviews. Therefore, the intervention and implementation are detailed in Chapter 6 of the results.

3.3 Research setting

This study was purposefully conducted in **public sector district level hospitals** in the Western Cape Metropole. This setting was identified as having the greatest need for understanding CDI by key stakeholders in SA. The study was designed to inform the development of a CDI quality improvement intervention to meet the context of low resource settings. This section details the unique aspects of the healthcare system in SA and the Western Cape province.

In 1994 the election of the African National Congress and Nelson Mandela as president of SA, ended apartheid, institutionalised segregation and discrimination in SA. The new government prioritised health equity. Quality healthcare and access became a component of the SA constitution and new policy with the National Health Plan.[189] Since the end of apartheid, substantial progress has been made to address immediate health needs, poverty and inequity.[190] Numerous facilities and programmes were developed to address health inequality. The 2004 National Health Act legislated a national health system including public and private sectors to provide equitable healthcare and established the district health system to provide primary care.[191]

Today the DoH, SA's public health system, serves a majority of the population (84%). While the private sector serves those who can afford it (16%). The cost to use the public health system is adjusted based on income with a sliding scale so that virtually anyone can access the health system, embodying a right to healthcare approach.[192] The first-line of access for healthcare are primary health clinics and community health centres. From the primary care facilities patients can be referred to the next level of care, the district hospitals. Patients use the clinics and district hospital closest to their home. The clinics and hospitals are distributed throughout each province. Finally, patients can be referred to the regional or tertiary hospitals for specialty care.[193] All levels are managed at the provincial level. At the national level policies are developed and implemented, while services from primary through tertiary care are managed by each province.

Yet, the quality of healthcare in SA is negatively impacted by numerous challenges. SA is afflicted by a quadruple burden of disease with high rates of:

- Communicable diseases (especially HIV and TB),
- Maternal and child mortality,
- Noncommunicable diseases (e.g., cardiovascular diseases and diabetes), and
- Injury and trauma.[194]

A recent review identified the following challenges facing SA:

- Unequal distribution of resources,
- Management and leadership crisis,
- Increased disease burden,
- Unregistered immigration, and
- Slow progress in restructuring the healthcare system, including strategies adopted by government to improve the quality of healthcare delivery.[36]

Although the public health system faces numerous challenges, the Western Cape province has the best health outcomes of the nine provinces in SA.[170] The province spends a higher proportion of its budget on healthcare, compared to other provinces.[192] It attributes the improved health outcomes to better access to healthcare as over 90% of the population can access healthcare within 30 min of their home. This is not the case in other parts of the country.[170]

However, the urban area surrounding Cape Town remains marked by the deep history of racial segregation and ongoing socio-economic segregation.[34] Urban planning spanning centuries separated populations by race with physical and geographic barriers. Today, informal settlements or townships remain. In the townships basic needs are compromised with poor access to electricity and shared water sources and toilets among multiple households.[33,195] Car ownership and limited public transportation remain a barrier to healthcare access in rural and urban areas of the Western Cape, if the district hospital or primary care clinic is not within

walking distance.[195] The Western Cape public health system serves these communities, along with other low-middle income households.

The Western Cape Department of Health and Wellness includes numerous facilities including 237 clinics, 24 district hospitals, five regional hospitals, one tertiary children's hospital, and two tertiary adult hospitals.[196] This thesis research was conducted within four of the public sector Western Cape district hospitals in the greater Cape Town metropole: Helderberg Hospital, Karl Bremer Hospital, Khayelitsha Hospital and Victoria Hospital. The intervention was implemented in three of these hospitals. The hospitals are medium in size, averaging 265 inpatient beds and serve the surrounding communities. While the hospitals are supported by the government, resources are limited. The four hospitals experience challenges cited in the literature, such as staff shortages across disciplines. Often, the public district hospitals are staffed primarily by early career doctors and registrars completing compulsory services, along with a few senior physicians or consultants that serve in a supervisory role. Pharmacy services are growing in SA; however, most pharmacists primarily serve a dispensary role. Nursing includes a variety of levels and specialties, such as staff nurses, ward managers, operations, and IPC. Also, many trainees in medicine, pharmacy and nursing from the Western Cape universities complete part of their training at the public district hospitals.

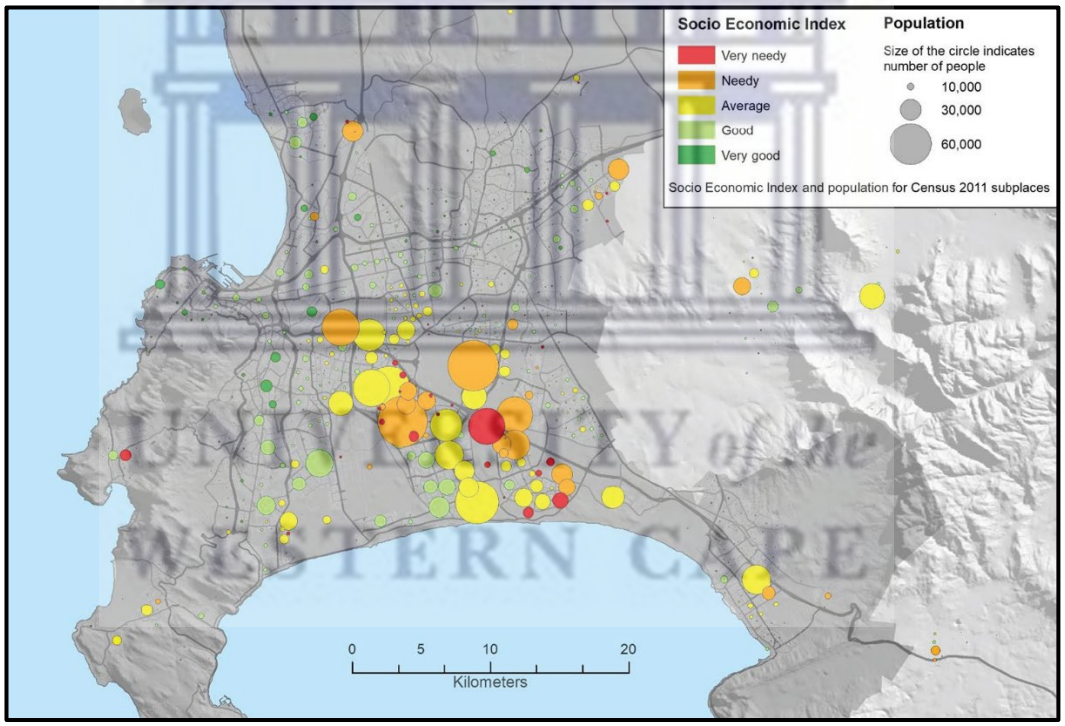
As introduced earlier, we focused this research at public district (secondary) level hospitals. This decision was informed by local infectious diseases leaders and the available data as detailed in the literature review. There was no information on the state of CDI at the district level, and limited studies previously conducted in SA were at the tertiary level.

Our approved research proposal included all district level hospitals in the Western Cape. Information about the study was shared with these sites. Of the 24 district level hospitals, four hospitals volunteered to participate. These hospitals tended to be hospitals with which the Western Cape School of Pharmacy already had existing

collaborations and connections with their pharmacy departments via pharmacy student training.

While the populations served among the four hospitals was comparable as they were all district level hospitals, they varied in their geographical location in the Western Cape. Socio-economic segregation remains in the Western Cape.[33-35] The Western Cape is the second most unequal province in SA according to the Western Cape Department of Health and Wellness, 2019 Burden of Disease Report. Figure 1 shows how levels of disparity cluster spatially in the Western Cape.[33]

Figure 1. Socio-economic index and population vary within the Western Cape, South Africa[a]

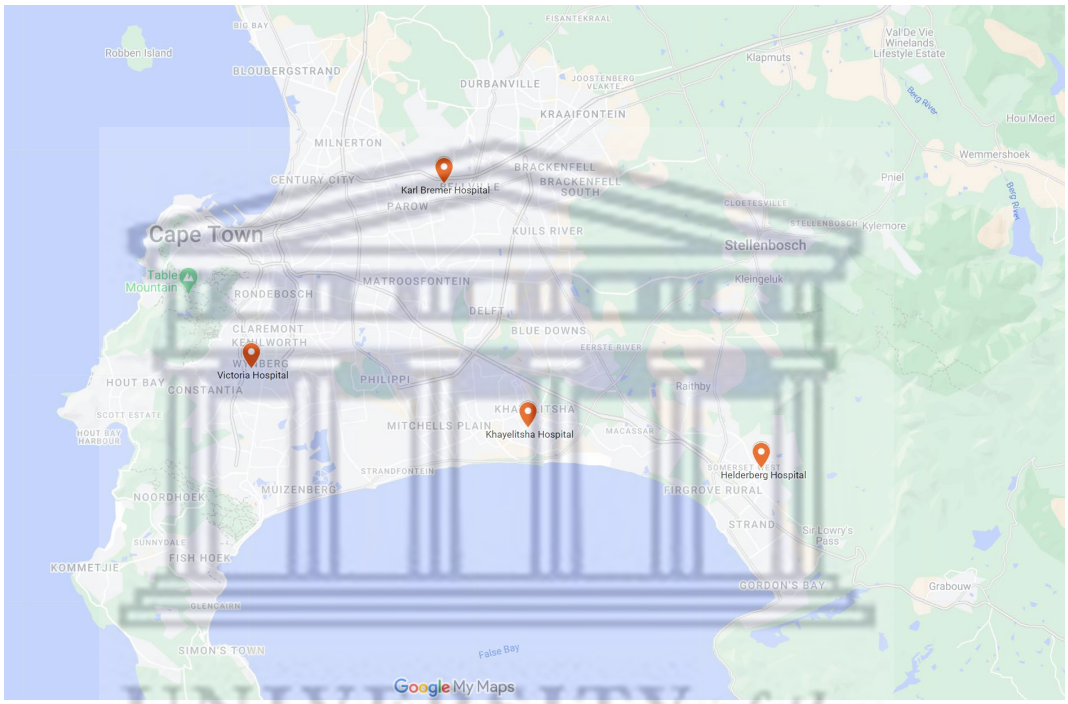


a. Source: Western Cape Department of Health and Wellness, 2019 Burden of Disease Report. https://www.westerncape.gov.za/assets/departments/health/burden_of_disease_report_2020.pdf

Figure 2 shows the location of each of the hospitals, created by the candidate with Google My Maps for this thesis. Distinguishing characteristics of the hospitals

include the following. Khayelitsha serves the district with the greatest socio-economic need, including a population with the greatest burden of age-standardised mortality.[33] Helderberg serves urban and rural patients. Victoria and Karl Bremmer are in closer proximity to the Cape Town city centre.

Figure 2. Four district level hospitals participated in the study in the Western Cape, South Africa.



3.4 Data collection and analysis methods

Methods and distinct considerations for collecting quantitative epidemiology and outcomes data, and qualitative interview data are described in this section. Specific parameters of the study methods and data analysis are included in the results chapters within the reproduced publications and corresponding methods sections. This section of the methodology chapter provides context on the choice of methods, reasoning applied to each approach, and details on data collection beyond the scope of the publications.

3.4.1 Sample identification

To collect the quantitative and epidemiology data, medical records from patients with a *C. difficile* laboratory result were reviewed retrospectively. Adult patients admitted to the approved secondary level public hospitals who had a *C. difficile* lab result during their hospitalisation were included. While the medical records in the public sector are primarily paper records, the NHLS keeps electronic results. We requested an electronic report of all patient record numbers with a *C. difficile* test at the hospitals included in our study. This allowed us to generate a list of the record numbers with positive results and a randomly-selected comparator group of patient folders with negative results. This approach determined our sample size and ensured the sample was feasible and representative of samples collected in 2015 at the four hospitals included in the study.

The NHLS data source was critical for identifying the sample population for the first objective. Without this electronic list, it would have been difficult to identify patients evaluated for CDI from the paper medical records alone. Alternatively, a prospective CDI study could have been designed, but would have required more time and resources to reach the same sample size we achieved with the retrospective review.

We designed the project to review all available patient folders with positive *C. difficile* results in 2015, the year prior to the commencement of data collection. As a comparator we reviewed a similar number of negative folders as it was not feasible to review all negative folders. The negative folders were randomly selected. Our results showed significant differences in CDI risk factors showing this approach and sample size was sufficient for studying risk factors associated with CDI. Therefore, this methods design balanced the capacity limitations of retrospective chart review with a one-year snapshot that included data from four sites to generate robust novel results.

We conducted semi-structured interviews with healthcare providers to garner a deep understanding of identifying, treating and managing CDI in SA. Interviews continued until a sample included multiple interviews with each type of provider. Interviews occurred at three of the four district level hospitals included in the quantitative baseline CDI data collection. The interviews and our qualitative coding process reached content saturation showing that we reached a representative sample of healthcare providers. We are certain that knowledge gaps in the treatment of CDI exist in public district level hospitals in the Western Cape. The supplies and resources available in the public district hospitals are like other low resource settings across sub-Saharan Africa. We can generalise our findings to additional low resource settings and similar settings where providers may not have had CDI included in their formal education. Three of the four hospitals in the epidemiology study volunteered to participate in the intervention and implementation.

3.4.2 Data collection tools

Three data collection tools supported high quality and consistent data collection: the CDI Data Collection Form (Appendix B), the CDI Data Collection Instructions Manual (Appendix C), and the Semi-Structured Interview Guide (Appendix D). Prior to beginning data collection, a data collection form and companion data collection manual were developed. Every data variable collected is included on the CDI Data Collection Form. The CDI Data Collection Instructions Manual served as a formal instructional document to increase reliability in data collection with the CDI Data Collection Form. The candidate and research team developed the qualitative data collection Semi-Structured Interview Guide prior to the interviews.

A final year international pharmacy student designed and drafted the data collection form and data collection manual with supervision and input from the candidate and supervisors. Data collected included demographic data, relevant comorbid conditions, illness severity indicators, diagnosis, antimicrobial use, lab test results, documented antimicrobial allergies, any previous history of CDI, clinical management and outcomes (Appendix B).

The research team piloted the CDI Data Collection Form with an example CDI patient case. This pilot of the data collection form helped to identify points on the form needing more clarity and to avoid discrepancies. The data collection form and data collection manual went through several iterations prior to beginning data collection to improve completeness and clarity of directions. As needed for each data variable, the data collection manual provides a clarification defining the data variable, details on the importance of the variable, and hints on the location in the medical folder where the variable might be found. This was especially important because the paper medical records often contain many documents and the order of these documents varied across folders. The data collection manual provided detailed instruction on various ways variables of interest could be documented in the paper chart (e.g., "Stool MCS"; MCS= microscopy, culture and sensitivity). The data collection form was first drafted as a text document and then created as a secure Google Form through the UW-Madison Google applications platform. During data collection, minor edits were made to the data collection form to create additional specific questions and reduce text box use when opportunities to do so were identified. The data items collected did not change from the items included in the original research protocol.

3.4.3 Data collection training

The candidate co-supervised a research group of six final year pharmacy students at the UWC and a pharmacy student from the UW-Madison. The candidate provided training on the data collection form and data collection manual in-person to these pharmacy students assisting with the data collection. The student research group focused on data collection at one of the four hospitals. The international pharmacy student from the UW-Madison contributed to data collection at one of the four hospitals. The candidate collected the data at the other two hospitals. An example patient case was used with the students to provide training on where to look for the items from the data collection form and how to use the data collection manual. During this data collection training simulation points of confusion were

identified by the students and clarified by the candidate with guidance on how to find more information about each variable with the data collection manual. During on-site data collection the candidate was available to answer additional questions from the students via a messaging application.

3.4.4 Data collection

Data were collected from patient clinical files (medical chart, prescription chart, order form and laboratory test results). Data were collected on-site at three of the hospitals. At the fourth hospital medical records were available electronically as scanned PDFs and were reviewed electronically. The international pharmacy student assisted with remote data collection. Data were collected on printed versions of the data collection form for later review and data entry through the Google form version of the data collection tool. Data collection forms were kept in a locked location at the School of Pharmacy. Data stored electronically was password protected.

Retrospective medical chart review is a timely process in all settings, but more so in low resource settings due to challenges with locating paper records and the information within the folder. Despite these challenges, the study was able to review over 250 records through the candidate's review and forming the research team of local SA pharmacy students and the international pharmacy student. The pharmacy students contributed to the data collection with supervision from the candidate and the candidate's supervisors and in co-ordination with course requirements for research projects. This research team was included in the ethics protocol.

Furthermore, handwriting may be difficult to read and local abbreviations may be unknown to external researchers. These challenges were overcome through consultation with the local healthcare providers at the time of data collection, such as the pharmacy staff at each hospital and insights from the local pharmacy research

team. Data were collected on the paper forms and verified for accuracy and completeness before entering the data electronically.

For the qualitative data collection, interviews with healthcare providers followed the semi-structured interview guide (Appendix D). The semi-structured interview format was chosen for the following strengths. The semi-structured format allowed for multiple elements of CDI management to be addressed and to have consistency of interview questions across interviews. The semi-structured format allowed for probing of details when a healthcare provider had more CDI knowledge or influence on the potential success of a CDI quality improvement intervention. This approach balanced reliability of our interview process with a wide range of CDI knowledge among healthcare providers. While patient interviews were included in the ethics approved methods and this interview guide, patients were not recruited due to resource limitations for the study scope.

Post-intervention implementation, data collection included a retrospective medical records review of patients hospitalised with *C. difficile* test orders during the 90 d post-implementation and followed the same data collection methods as the baseline epidemiology study. All patient folders with a positive *C. difficile* result and a random sample of the negative results were reviewed. Patient outcomes and checklist components (e.g., antibiotics) were collected. Qualitative interviews and focus groups were conducted with healthcare providers on-site. These interviews followed the original semi-structured interview guide plus questions about the intervention. Audio files were processed and thematically coded with the same methods as pre-intervention interviews. Content saturation was reached.

3.4.5 Ensuring data validity and reliability

To increase data validity, the following steps were taken to ensure the data collected measured the variables of interest during a *C. difficile* hospitalisation. The methods included matching the *C. difficile* test results from the NHLS records with hospitalisation records, to collect data on risk factors, identification, treatment,

outcomes, and other management criteria. Records were requested only by the patient's medical number. The record, a collection of folders and documents, returned could be missing key documents or components. The physical folder could include medical records that were from a different hospitalisation of interest. Conversely, the record could include multiple thick folders that were not necessarily organised by date. To increase data reliability in the student data collection group a peer would review the data collection form prior to data entry and re-visit the patient medical record to clarify any confusion on the data collection form. This process reduced missing information.

The following process was followed during data cleaning and processing to increase data validity. Collected hospitalisation data and dates from the medical records were compared with laboratory data dates from the NHLS to identify any outliers. Then, laboratory results outside the hospitalisation dates were investigated to ensure the data collected was from a hospitalisation that included the *C. difficile* query. (i.e., the query was not from a different hospitalisation or outpatient visit). A portion of the *C. difficile* patients were discharged or died in hospital before a result was final, but the test was ordered during the hospitalisation. Other outliers of laboratory dates indicated a mismatch in the hospitalisation and laboratory test, and subsequently the hospitalisation data were excluded.

To reduce bias and increase the reliability of qualitative results a comprehensive approach was used. The candidate provided training to pharmacy students assisting with the research and qualitative data analysis. Audio files were transcribed verbatim by the candidate and pharmacy students from the UW-Madison. The de-identified transcripts are available by request.

3.4.6 Analysis

Demographic data were analysed by calculating univariate summary statistics. Summary statistics were calculated for patient management criteria. Patient characteristics and CDI risk factors were analysed with X^2 tests by *C. difficile* test

result. *P* values less than or equal to 0.05 were considered significant. A survival analysis comparing patients with *C. difficile* positive and negative results was performed with the Gehan-Breslow-Wilcoxon test. A univariate mortality analysis was performed. A multivariable logistic regression was performed to determine independent predictors of all-cause mortality.

Interviews with healthcare providers were transcribed verbatim and coded for a priori and emerging themes with the qualitive data analysis software NVIVO (Version 11, QSR International). As mentioned and described in the publication chapter, each transcript was coded by two individuals and codes were compared to identify and resolve any discrepancies. A novel method of calculating knowledge scores was created based on seven primary components of CDI that were addressed in the interviews. Knowledge scores were summarised descriptively with a median score (0 to 7) and interquartiles across all interviews and by profession.

The candidate and the two assisting UW-Madison pharmacy students completed a training course on coding qualitative data with NVIVO software. These two individuals, pharmacy students different than the candidate, coded the transcripts to a priori themes and emerging themes with guidance and supervision from the candidate. These two students earned independent study credit for their contributions to the qualitative research.

Discrepancies in coding were discussed among the two coders and the candidate until a resolution on the coding was achieved. This process was time-consuming with transcription rates averaging a fourfold transcription to audio duration ratio, the result is a detailed coded analysis of provider perceptions and practices surrounding IPC and CDI. This qualitative dataset provides new insights and a groundwork for quality improvement interventions related to this CDI project and future work related to IPC and AMS.

The CFIR and the FRAME-IS frameworks were applied to collected data and observations to identify drivers and barriers to implementation and understand

differences in uptake. As described in the literature review, CFIR is a meta-theoretical framework. Details on how these frameworks were applied are included in the results (see Chapter 6). The CFIR technical assistance website was helpful in the analysis (www.cfirguide.org). For each of the 39 constricts, the website provided a short and detailed description, inclusion and exclusion criteria, and references.[197]

In summary, the methodology for data collection and analysis was developed with considerations and approaches to minimise bias. The retrospective review of patient folders with a *C. difficile* result, pre- and post-intervention, included a random selection of negative results to minimise selection bias. The random sample of patients had diarrhoea without CDI. To minimise confirmation bias from the candidate, the qualitative component of the research included paired data coding by team members other than the candidate and a process to resolve discrepancies.

3.5 Ethics considerations

This human subject research was conducted in accordance with the approved research protocol and the following ethical considerations. First, this study's conduct was approved by the Humanities and Social Science Research Ethics Committee, Department of Research Development of the UWC (Ethics Reference Number: HS/16/1/24) (Appendix E). Second, the study was registered on the South African National Health Research Database (Reference Number: WC_2016RP2_170). The NHLS approved the study (Appendix F). Third, each participating hospital approved the study proposal following the ethics committee and provincial and national level approvals. This study was conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines, whichever afforded the greater protection to the subject.[198,199] The research applied ethics principals from the Belmont Report: respect for subjects, beneficence and justice.[200] The local ethics committee review serves to protect the rights and welfare of human subjects.[201]

3.5.1 Respect for persons: Consent and confidentiality

Information about the study purpose and interview duration was communicated to potential participants by the research team. Informed consent was sought under conditions without unduly influence (e.g., supervisor presence). Key informant interview participants, healthcare providers and administrators, provided signed written informed consent about their voluntary confidential participation. Consent forms included information on what the interview would be about, and a separate consent line for permission to audio record the interview before the interview began (Appendix G). Participants were informed of their rights to participate voluntarily and withdraw from the project at any time without penalty. The ethics committee approved the retrospective patient data collection without patient consent as no specific change to a patient's treatment was included in the research design.

All data collected remained confidential and secure. Data collection forms were kept in a locked location at the School of Pharmacy and data stored electronically was password protected. Protection of data confidentiality was increased with the use of project-coded identifiers; patient and participant identification details were linked to a project code and the key was kept separately from the research data. Unnecessary identifiers (e.g., patient names) were not included in data collection. Results reported to the participating hospitals and prepared for presentation, including conferences and publications, were aggerated to protect individual identities.

3.5.2 Beneficence, justice and fairness

Consistent with the ethical principal beneficence, the study methods were designed with the intention to maximise benefit and minimise harm, as a quality improvement study.[200-202] The study aimed to improve the quality of care provided to patients admitted with or who develop diarrhoea during their hospitalisation by first establishing a baseline of provider CDI awareness and current management, and then developing a context informed CDI intervention. Considering risk, there

was no anticipated discomfort for those contributing to this study, nor did any participants appear adversely affected by the study. In terms of justice and fairness, the study was designed to fairly distribute the risks and benefits of the research across groups participating in the research and society.[202] The study results were reported to the participating hospitals and the SA DoH. The results are publicly available through publication in peer-reviewed international journals to inform treatment guidelines, policy development, and quality improvement interventions globally.

3.6 Funding

Funding for administrative functions was provided by the School of Pharmacy, UWC. The candidate was supported by the Living the Wisconsin Idea fund held at the UW-Madison School of Pharmacy. Travel expenses from the US to SA, cost of living expenses in SA, and some research expenses (e.g., speciality printing) were supported by this financial gift account. The conduct of the research was responsibility of the candidate and research team. The research team operated independently in designing the study, interpreting the data, writing, and publishing the results.

4 RESULTS: EPIDEMIOLOGY AND OUTCOMES

This chapter begins the presentation of study results. Each of three results chapters is supported by a manuscript. Thesis findings in Results Chapter 4 and Chapter 5 are already published in international peer-reviewed journals. Results Chapter 6 is accepted for publication in an international peer-reviewed journal.

4.1 Reasoning

As previously described, the reasoning for this study was that CDI epidemiology and outcomes were previously unknown in sub-Saharan Africa to our knowledge. CDI baseline data were necessary to evaluate future quality improvement interventions.

4.2 Publication attributes

This thesis chapter includes a reproduction of the study that has been published in *BMJ Global Health* as:

Legenza L, Barnett S, Rose W, Bianchini M, Safdar N, Coetzee R. The epidemiology and outcomes of *Clostridium difficile* infection among hospitalised patients in South Africa: results of a multicenter retrospective study. BMJ Global Health. 2018;3:e000889. PMCID: PMC6058171

As described earlier in the Outline (1.9), reference citations from the publication are listed at the end of the manuscript, numbered in order of appearance.

The final PDF of the publication is provided in thesis Appendix H and author guidelines for *BMJ Global Health* are provided in thesis Appendix I.

BMJ Global Health is accredited by the Department of Higher Education and Training (DHET) in South Africa. The journal is Medline indexed and peer-reviewed with a 2020 Journal Citation Reports (JCR) Impact Factor of 5.558.

Seven PubMed indexed articles cite this publication according to iCite from the United States National Institutes of Health (NIH). The publication is cited by 12 documents in Scopus, an abstract and citation database of peer-reviewed literature. Documents in the Web of Science Core Collection cite this publication 10 times. According to Google Scholar the article is cited online 17 times.

Notably, experts from the World Society of Emergency Surgery (WSES) cite this publication in its opening statement of the '2019 update of the WSES guidelines for the management of *Clostridioides (Clostridium) difficile* infection in surgical patients,' describing the global severity of CDI.[203] The WSES guidelines have 39,000 accesses and have been cited by 50 articles, according to Web of Science. A study on CDI patients attending a tuberculosis hospital in South Africa cite this publication's novel identification of tuberculosis as an independent risk factor for CDI.[204] The International Society for Infectious Diseases published an expert position paper on CDI in hospitals in 2020 and included the CDI risk factors identified in this chapter for their CDI in Africa section.[7] A 2022 review paper of CDI in Africa also cites this publication for identifying tuberculosis as a risk factor for CDI.[205]

4.3 Contributions

The candidate, Laurel Legenza was the primary contributing author of the study. Renier Coetzee, the candidate's supervisor is the corresponding author. Contributions to the paper are published as follows: "LL designed the study, designed data collection, monitored data collection for the whole study, collected data, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. She is the guarantor of the study. SB, WR and NS provided guidance on the study and revised the paper. MB designed data collection tools,

collected data and revised the paper. RC facilitated the collaborative project between the University of the Western Cape and the University of Wisconsin, provided guidance on the study and revised the paper." All co-authors provided feedback and approved the final version of the publication.

4.4 The epidemiology and outcomes of *Clostridium difficile* infection among hospitalised patients in South Africa: results of a multicenter retrospective study

Laurel Legenza
University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, Wisconsin 53705, United States
Comparative Health Systems Global Pharmacy Fellow

Susanne Barnett
University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, Wisconsin 53705, United States
Associate Professor

Warren Rose
University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, Wisconsin 53705, United States
Associate Professor

Monica Bianchini
University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, Wisconsin 53705, United States
Pharmacy Student

Nasia Safdar
University of Wisconsin School of Medicine and Public Health, 750 Highland Ave, Madison, Wisconsin 53726 United States
Associate Professor

Renier Coetzee
University of the Western Cape, Robert Sobukwe, Cape Town, 7535 South Africa
Senior Lecturer

Correspondence to: Renier Coetzee recoetzee@uwc.ac.za Phone: + 27 021 959 3665
Fax: + 21 021 959-3407

Word count: 4,149 words

Abbreviations

CDI *Clostridium difficile* infection

NHLS National Health Laboratory Service

PCR Polymerase chain reaction

Abstract

Introduction

Limited data exists on *Clostridium difficile* infection (CDI) in low-resource settings and settings with high prevalence of HIV and. We aimed to determine baseline CDI patient characteristics and management and their contribution to mortality.

Methods

We reviewed adult patients hospitalised with diarrhoea and a *C. difficile* test result in 2015 from four public district hospitals in the Western Cape, South Africa. The primary outcome measures were risk factors for mortality. Secondary outcomes were *C. difficile* risk factors (positive vs. negative) and CDI treatment.

Results

Charts of patients with diarrhoea tested for *C. difficile* (N=250; 112 *C. difficile* positive, 138 *C. difficile* negative) were reviewed. The study population included more females (65%). *C. difficile* positive patients were older (46.5 vs. 40.7 years, P<.01). All cause mortality was more common in the *C. difficile* positive group (29% vs. 8%, P<.0001; hazard ratio 2.0, 95% CI 1.1-3.6). Tuberculosis (*C. difficile* positive 54% versus *C. difficile* negative 32%, P<.001), 30-day prior antibiotic exposure (*C. difficile* positive 83% versus *C. difficile* negative 46%, P<.001), and prior hospitalisation (*C. difficile* positive 55% versus *C. difficile* negative 22%, P<.001) were also more common in the *C. difficile* positive group. *C. difficile* positive test result (OR 4.7, 95% CI 2.0-11.2; P<.001), male gender (OR 2.8, 95% CI 1.1-7.2; P=.031), and tuberculosis (OR 2.3, 95% CI 1.0-5.0; P=.038) were independently associated with mortality. Of patients starting treatment, metronidazole was the most common antimicrobial therapy initiated (70%, n=78); 32 *C. difficile* positive (29%) patients were not treated.

Conclusion

Patients testing positive for *Clostridium difficile* are at high risk of mortality at public district hospitals in South Africa. Tuberculosis should be considered an additional risk factor for CDI in populations with high tuberculosis and HIV comorbidity. Interventions for CDI prevention and management are urgently needed.

What is already known about this topic?

Patients in South Africa have significant comorbidities distinct from high resource countries, including a higher incidence of HIV and tuberculosis, which may uniquely increase patients' risk for *Clostridium difficile* infection (CDI).

What are the new findings?

This study is the first examining risk factors, management, infection control, and mortality among hospitalised patients in public hospitals in sub-Saharan Africa to our knowledge.

The majority of patients treated for CDI received metronidazole, while the mortality of patients with a *C. difficile* positive result was significantly higher than similar patients testing negative with diarrhoea.

In populations with high tuberculosis and HIV comorbidity, tuberculosis is an additional risk factor for CDI.

What do the new findings imply?

Vancomycin should be considered as an alternative to metronidazole in populations with high prevalence of tuberculosis and immunocompromising conditions as a high mortality rate was observed in this study.

Introduction

Clostridium difficile infection (CDI) is an increasing global health concern resulting in severe diarrhoea, excessive healthcare costs, readmissions, and mortality. Life-threatening complications resulting from CDI include sepsis, pseudomembranous colitis, and toxic megacolon. The majority of CDI studies have been conducted in high resource countries.[1] CDI incidence increased yearly in these settings after 2000 until recently; a decline in CDI incidence from 2011-2015 in long-term care settings was reported in association with decreased hospital fluoroquinolone use and detection of the NAP1/027 strain.[1 2] *C. difficile* remains the most common pathogen implicated in hospital-acquired infections in the United States.[3 4] CDI in patients is associated with antibiotic use, which leads to disruption of normal flora and uninhibited growth of toxigenic *C. difficile*.[5] Antibiotics commonly associated with CDI include fluoroquinolones, third-generation cephalosporins, clindamycin, and penicillins.[6] Advanced age is not only a noted risk factor for CDI, but also commonly associated with CDI mortality in high-resource countries.[7] Additional risk factors for CDI include hospitalisation, inflammatory bowel disease, immunodeficiency, organ transplantation, chemotherapy, gastric acid suppression, chronic kidney disease, and exposure to individuals with *C. difficile*.[6] The healthcare environment and patients in low resource settings are distinct from high resource settings. For example, South Africa has the lowest life expectancy in the world, 49.7 years, reducing the likelihood for elderly age to be a CDI risk factor.[8] Meanwhile, the relationship of CDI and the infectious diseases associated with mortality in this population is understudied. Thus, further investigation of CDI risk factors in these countries is urgently needed.

In South Africa, the leading causes of death are infectious diseases including tuberculosis, influenza/pneumonia, and HIV, which may uniquely increase patients' risk for CDI.[9 10] South Africa has the largest known HIV epidemic in the world. Adult prevalence is estimated to be 18.9% and 19% of people living with HIV globally reside in South Africa.[11] Tuberculosis incidence in South Africa is the sixth highest globally. Coinfection of tuberculosis in patients with HIV is a

synergistic epidemic, including a disproportionate rate of HIV-associated tuberculosis deaths as 63% of tuberculosis cases are in patients with HIV.[12 13] Over the past decade, tuberculosis has surpassed HIV and cardiovascular disease as the leading cause of death.[14] While CDI studies in Africa are limited, two previous studies at a tertiary hospital in Cape Town, South Africa, documented 9-22% of patients with diarrhoea tested *C. difficile* positive using different methods.[15 16] In one of these studies, patients with *C. difficile* positive results were associated with antibiotic use in the previous 28 days and hospitalisation within the previous 90 days compared to patients with negative results.[15] The prevalence of the NAP1/027 strain was 3.4%, which is substantially lower than in high resource settings such as the United States, which has ranged from a 16.9-26.2% prevalence in recent studies.[15 17]

Understanding the epidemiology of CDI in low-resource settings is essential to improve identification, prevention, and treatment measures. In the present study, we identify patient CDI characteristics and management in resource-limited public district level hospitals and their contribution to mortality.

Methods

Local infectious disease leaders were consulted early in study design, starting in August 2015. These leaders identified CDI as a critical public health challenge in South Africa because of its increasing incidence and high morbidity and mortality globally, lack of local studies, and vulnerable populations with HIV and tuberculosis locally. In addition to the lack of CDI studies performed in these hospitals and this patient population, focus on district hospitals was also recommended due to the scarcity of CDI data at this level. Subsequently the University of the Western Cape Research Ethics Committee, National Health Laboratory Service (NHLS), and Western Cape Department of Health granted approval for the first CDI epidemiological study in South African district level hospitals.

Upon approval, a multicenter, retrospective chart review was conducted at four district level hospitals, averaging 265 inpatient beds, in Cape Town, South Africa. The study included hospitalised adult patients (>18 years of age) with diarrhoea and either a positive or negative *C. difficile* polymerase chain reaction (PCR) test result from one or more stool samples during the year 2015. These patients were identified from a list of *C. difficile* test results provided by NHLS, which is a national network of diagnostic laboratories that serve 80% of the South African population, including the Western Cape Department of Health hospitals. All stool samples from the district level hospitals included in this study were sent to the NHLS laboratory at the nearest tertiary level hospital. Standardized NHLS protocols indicated PCR testing for all eligible samples in 2015 (NHLS does not perform *C. difficile* tests on solid stool samples or patients with a recent *C. difficile* positive result). All patients included in the study had diarrhoea that took the shape of the container and clinical suspicion for CDI. A minimum number of stools within 24 hours was not required for study inclusion as frequency was inconsistently documented. Any additional etiologies tested were not included in the laboratory report. Test results originating from pediatric patients, outpatient clinics, or day surgery patients were excluded. Patients with tests ordered in the emergency department were included if the patient was subsequently admitted to the hospital.

The primary outcome of this study was the identification of risk factors for mortality in South African patients in the Western Cape with diarrhoea. Secondary outcomes were risk factors for a *C. difficile* positive result compared to a *C. difficile* negative result, and within this group, risk factors for mortality and management of CDI.

The 2015 medical records for any patient with a *C. difficile* test result were reviewed August 2016-April 2017. Data collection was subject to the available processes for medical record review and availability of files at each individual hospital. Paper folders were requested from the medical records department at each hospital and reviewed by study personnel onsite. At one hospital, medical records were accessible electronically by access granted to view scanned files of the patient folders remotely. The review included all available patient records with a positive

C. difficile test result. At each hospital, an equal number of *C. difficile* positive and negative patient charts were requested and reviewed if available. At most hospitals, the number of negative test results was much larger than positive results. Therefore, all identified patients with a positive *C. difficile* test result were requested, while patients with a negative test result were randomly selected following an auto-generated random number process. The randomization of the negative chart numbers was performed to address selection bias. If the total number of patients tested at each hospital was less than 25 patients, all available charts were reviewed. As this is the first epidemiologic study in district level hospitals, the magnitude of tests was difficult to predict. In this study design, the number of positive results limited sample size during the year evaluated and an a priori sample size calculation was not performed.

Use of a structured data collection tool allowed for review of all clinical and laboratory notes available in the medical record from the hospital admission including the *C. difficile* test. Pertinent records prior to the admission were also reviewed using the same tool to determine past medical history and previous antibiotic exposure, and post admission records were reviewed to determine patient outcomes, recurrence and mortality. Data collected included demographics (gender, age, allergies), comorbid conditions (HIV, tuberculosis, multidrug resistant tuberculosis, diabetes, cardiovascular conditions: heart failure, hypertension, hyperlipidemia, other cardiovascular conditions, malignancy, inflammatory bowel diseases: ulcerative colitis, Crohn's, other immunocompromising condition), hospitalisations prior to the current admission (0-30 and 31-90 days prior to test order) and previous antibiotic exposure, including a single dose (penicillins, quinolones, carbapenems, cephalosporin, clindamycin, or other), and indication in prior 30 days and 90 days from date of written CDI order, prior CDI history (current episode is documented as first CDI episode, recurrence, unknown if first episode or recurrence), clinical presentation (diarrhoea, temperature [>38 C], hematochezia, pseudomembranous colitis), dates of admission, rehydration, loperamide use, CDI antibiotic treatment, CDI-related infection control (isolation and contact precautions), and reason for hospitalisation.

Data was analyzed using Stata SE statistical software (Version 15.0, StataCorp, College Station, Texas, USA). Summary statistics for infection management were determined, including antibiotic treatment and infection prevention and control components. Length of stay was summarized and compared by t-tests both by *C. difficile* test result and hospital mortality to express mean, median, and statistically significant differences. Univariate summary statistics were calculated for age and gender of individual patients. Chi-squared tests were conducted by *C. difficile* test result and mortality for patient characteristics and CDI risk factors. A survival analysis with the Gehan-Breslow-Wilcoxon test was determined for patients with *C. difficile* positive PCR versus *C. difficile* negative PCR in GraphPad Prism (Version 6, GraphPad Software, La Jolla, California, USA), with a start date equal to when an order for *C. difficile* test was written and end date the day of mortality or discharge. Censoring occurred for patients discharged before 30 days to account for uncertainty of survival and readmission post discharge. Patients with a clinic visit or hospital admission occurring greater than 30 days after the *C. difficile* test were categorized as survivors. P-values ≤.05 were considered significant. All variables identified as at least marginally significant (P<.10) predictors in the univariate mortality analysis were included in the model. Independent predictors of all-cause mortality were determined via a separate multivariable logistic regression.

Results

Overall, 652 *C. difficile* PCR tests were conducted in 2015 from the four hospitals included; 19 of these had an error result and were excluded. Forty-one of the 291 patient charts requested were excluded because either the patient chart was unavailable or missing, the chart lacked adequate documentation to review related to the test date, or the test met exclusion criteria for not occurring during a hospitalisation (e.g. outpatient clinic, day surgery). Of 139 positive results, 112 results and corresponding charts were reviewed and of 494 negative results, 138 negative results were reviewed (Total n=250; Figure 1). Two tests were reviewed for one patient during a 76-day length of stay. All other test results reviewed were

from unique hospitalisations. The 250 test results reviewed represent 225 individual patients.

Patient characteristics analyzed by test result in the univariate analyses are presented in table 1. Significant differences were found in the patient demographics in patients testing positive versus negative for *C. difficile* including age, tuberculosis, prior hospitalisation, and specific antibiotic use. Mean age and gender distribution was calculated for 225 individual patients (102 *C. difficile* +; 123 *C. difficile* -), excluding subsequent test results from patients with more than one test in the study period. The mean age for the *C. difficile* positive patients was 46.5 years compared to 40.7 years for *C. difficile* negative patients (P<.01). There were more females in the study population (65%). However, mean age was similar between men and women in this study overall (43.4 vs. 43.3 years, respectively).

Presence of comorbid infectious diseases also proved to be a significant variable, particularly with regard to tuberculosis. More patients testing positive for *C. difficile* also had tuberculosis (*C. difficile* positive 54% versus *C. difficile* negative 32%, P<.001). HIV rates were high in both *C. difficile* positive and *C. difficile* negative patients (71% versus 80%, respectively; P=0.07). Of HIV positive patients with a *C. difficile* test result, the majority had CD4 counts consistent with acquired immunodeficiency syndrome or AIDS (CD4 count <200 cells/μL; *C. difficile* positive 81%; *C. difficile* negative 81%; n=178).

Analysis of *C. difficile* test results confirmed prior hospitalisation and antibiotic exposure are important CDI risk factors among patients included in the study. Recent prior hospitalisation was more common in *C. difficile* positive patients for both hospitalisation 30 days prior and 90 days prior to the admission (P<.001). Thirty-day prior antibiotic exposure to all antibiotic classes reviewed was significantly higher in the *C. difficile* positive group (table 1). The most common antibiotic class with recent prior exposure to patients tested for *C. difficile* was cephalosporins, with half of *C. difficile* positive patients receiving a cephalosporin in the 30-days prior to the *C. difficile* test order (versus 34% in *C. difficile* negative,

P<0.02). Documentation of tuberculosis antibiotic treatment prior to admission was insufficient to report as prior tuberculosis treatment was not consistently detailed for patients with treatment ordered in hospital. Prescriptions outside the hospital and onsite clinic were not captured if not noted in the admission clinical notes.

Mortality in patients with diarrhoea was more common in the *C. difficile* positive group (29% vs. 8%, P<.0001). A Kaplan-Meier survival analysis (P=.0087) for patients evaluated following a *C. difficile* test order (Figure 2) found an all-cause mortality hazard ratio of 2.0 (95% CI 1.1-3.6) in patients with a *C. difficile* positive test. All mortality identified occurred in-hospital.

Variables with marginal associations (P<.01) with mortality are presented in Table 2. A logistic regression including these variables, 30-day mortality, *C. difficile* test result, prior hospitalisation (30-day and 90-day), critical care admission, tuberculosis, sex, multi-drug resistant tuberculosis, and hematochezia was performed (Table 3) for mortality as a dependent variable. HIV, immunosuppression, and malignancy did not meet criteria for inclusion in the model. Multi-drug resistant tuberculosis perfectly predicted mortality, so the variable was dropped from the model (n=12). An independent risk of mortality in patients with diarrhoea with a *C. difficile* positive test result versus *C. difficile* negative test (OR 4.7, 95% CI 2.0-11.2; P<.001) was found. Clinically meaningful independent variables associated with mortality also included comorbid tuberculosis (OR 2.3, 95% CI 1.0-5.0; P=.038) and male sex (OR 2.8, 95% CI 1.1-7.2; P=.031). Prior antibiotic exposure overall or with any specific antibiotic class and hospitalisation were not independently associated with mortality.

Components of *C. difficile* management for the *C. difficile* positive patients were assessed (n=112). Intravenous rehydration was widely provided (95%) but oral rehydration was rarely documented (12%). Contact precautions were documented for 36% of patients. Of the 21% of patients with a *C. difficile* positive result who were allocated to an isolation room, 16 of these 24 patients (67%) were also diagnosed with comorbid tuberculosis. Loperamide, contraindicated in CDI, was

administered to 44% of all patients reviewed, which includes 41% of *C. difficile* positive and 46% of *C. difficile* negative patients. Loperamide was discontinued after documentation of a *C. difficile* positive result in 22% of these patients.

Twenty-nine percent of *C. difficile* positive patients did not have documented treatment. Explanations observed for lack of treatment included patient improvement (n=2, 15%), no follow-up or documentation of *C. difficile* test result during admission while the result was finalized on a date the patient was still hospitalised (n=8, 25%), patient discharge or transfer before test result finalized (n=13, 41%) and mortality before result finalized (n=6, 19%). Metronidazole was the most common antimicrobial therapy initiated (70%, n=78). Metronidazole strength was most often 400 mg (95%) for initial treatment and usually ordered every eight hours (97%), consistent with the South African Standard Treatment Guidelines.[18] Treatment durations, however, varied from the 10-day guideline recommendation. Duration of initial metronidazole therapy ordered ranged from 5-days to 14-days, with 10-days being the most commonly prescribed (45%). Metronidazole orders less than or equal to 7-days were written for 30% of patients. *Clostridium difficile* antibiotic treatment prescribing rates were not significantly different across the four hospitals.

Two patients were treated with oral vancomycin monotherapy for initial treatment. Vancomycin was added to or replaced metronidazole treatment in 14.3% of patients (n=16). When oral vancomycin was added, the frequency of administration was consistent with every six hours as per South African Standard Treatment Guidelines for CDI in 47% of orders.[18] The most common duration of vancomycin was ten days (44%) and ranged from 5-15-days (31% < 7-days). All initial CDI treatment was ordered for oral administration. Intravenous vancomycin was added to metronidazole in two patients (dose 600 mg and 1000 mg once daily), but we were unable to document whether this vancomycin administration might have been for CDI management or another infection. One patient was changed from oral to intravenous metronidazole for three doses, then changed back to oral administration.

Overall, mean length of stay (LOS) for all hospitalisations reviewed was 10.2±11.0 days (median 7 days, range 0-76 days). Mean LOS for *C. difficile* positive patients discharged from the hospital was significantly longer (11.3±10.5 days, median 9 days) compared to *C. difficile* negative patients (8.2±8.5 days, median=6.5 days, P=0.02). Recurrence could not be accurately assessed on all patients due to inconsistent records before and after the admission evaluated.

Discussion

Although there is a wealth of data on CDI epidemiology and outcomes from high resource countries, research from low resource countries is sparse. This analysis and these data are the first examining *C. difficile* infection, risk factors, management, and mortality among hospitalised patients in South Africa at district level hospitals to our knowledge. Understanding how CDI is currently being treated and which patients are at greatest risk in South Africa is the first step to designing and implementing quality improvement interventions. Prevalence of tuberculosis appears to be strongly associated with CDI incidence and to interact with demographic and other risk factors influencing positive *C. difficile* results and mortality. Significantly more patients in our study who tested positive for *C. difficile* had tuberculosis (P<.001). *C. difficile* positive test result, tuberculosis, and male sex were found to be independent risk factors for 30-day mortality in this study. Consistent with known CDI risk factors in high resource settings, prior hospitalisation and antibiotic exposure was strongly associated with a positive *C. difficile* test result. Tuberculosis should be considered a risk factor for CDI in this population, as associations and mortality outcomes in this study are revelatory. Tuberculosis is a less critical risk factor in high resource settings where prevalence is low. Targeted CDI interventions may improve the high mortality identified and apply to similar low resource settings in the future.

A post hoc power analysis of *C. difficile* result and mortality for our sample size, 112 *C. difficile* positive results and a 138 *C. difficile* negative results was performed.

The calculated effect size of 0.27 indicated we had 99% power to detect this difference. However, it may be difficult to extrapolate these findings to patients treated in the private sector in South Africa, where HIV and tuberculosis prevalence are significantly lower. A weakness of this study includes the limitations of the retrospective design and data. The chart review included primarily hand written clinical notes that occasionally required interpretation; assistance from local collaborators and study team members was essential in the data collection phase. The data collection was also limited to only information included in the patient charts. For example, prior antibiotics and hospitalisations at institutions other than a patient's local hospital would be missing, as would any paper records not properly combined or available during data collection. Furthermore, information bias from any missing data regarding severe infections or severe comorbidities such as cancer could affect the results. The study data is insufficient to delineate if the association of CDI and tuberculosis is due to disease pathogenesis or antibiotics administered for tuberculosis. Patients were unable to be evaluated for severe disease as defined by CDI consensus guidelines as laboratory data was often limited in this retrospective review. It is possible, however, that many patients in this study may have had severe CDI as evidenced by the high mortality rate of *C. difficile* positive patients, independent of other variables. Despite the limitations of this study, we are reporting novel, needed, and independently associated factors of significance.

The results of this study indicate key differences relating to CDI risk factors and mortality between high and low resource countries, specifically regarding associations of CDI to tuberculosis, sex, age, and antibiotic exposure. First, tuberculosis is not commonly included in a list of risk factors for CDI, as this infection is relatively infrequent in high resource countries where CDI has been most studied. The associations of tuberculosis and CDI could be related to prior healthcare exposure and the use of second line tuberculosis antibiotics, including fluoroquinolones. A study conducted at tertiary hospitals in South Korea found an increased risk of mortality in patients with concomitant CDI and tuberculosis, compared to CDI alone.[19] This suggests there may be a pathophysiologic or antibiotic induced relationship between CDI and mortality in patients with

tuberculosis. Second, data on sex/gender differences in CDI associated mortality are limited. Two previous studies implicate male sex with CDI and complications. The first is a study limited to a single center in France identifying male sex as a predictor of severe CDI. Another is a study that reported male patients with proton pump inhibitor use have a higher risk of CDI mortality.[20 21] Tuberculosis incidence is higher in males in South Africa (male 226,000 vs. female 154,000) and a tendency for men to present for healthcare later in their disease course has been reported in South Africa and globally.[22 23] Despite the propensity for CDI-related mortality in males, previous studies in high resource settings report females are more likely to have CDI.[7 24] Therefore, distinct CDI associated risks may exist between men and women. Third, tuberculosis infection may also be a factor in the age of patients hospitalised with CDI in low resource settings. The relatively young average age of patients included in this study likely reflects the population burden of high tuberculosis incidence in South Africa in the age range of 25-44 years.[22] Finally, the antibiotic exposure observed in this study resembles patterns observed in England prior to prescribing patterns to control CDI, an element of antimicrobial stewardship.[25] In addition to continued strengthening of antimicrobial stewardship efforts in South Africa, significant differences discussed in this manuscript highlight the need for population tailored CDI guidelines, including identification of population specific CDI risk factors and interventions.

Using the results of this study, clinicians and policymakers in areas with a high prevalence of tuberculosis and HIV should carefully evaluate which patients are at highest risk for a poor outcome from CDI and ensure appropriate initial treatment. The high mortality associated with CDI in this study also highlights the need for prompt identification, appropriate treatment, and infection prevention and control measures in populations with high HIV and tuberculosis prevalence. The 2010 CDI Infectious Diseases Society of America guidelines recommended first-line therapy with oral metronidazole for mild to moderate disease. Since publication of these guidelines, further studies have supported the use of vancomycin as a first-line therapy. Subsequently, the 2017 guidelines now restrict metronidazole to initial non-severe CDI, when other therapies are contraindicated or unavailable.[26] The

majority of patients treated for CDI in this study received metronidazole, and were switched to vancomycin only if initial therapy with metronidazole was proven ineffective. The high mortality rate of CDI patients in our study suggest that South African patients may benefit from first line vancomycin therapy as this medication has been shown to have higher clinical cure rates and significantly lower risk of mortality in severe CDI.[27 28] If oral vancomycin therapy is not adopted as first-line, CDI antibiotic treatment decisions should include markers beyond white blood cell count, especially for immunocompromised patients and in settings where laboratory results are limited. Risk classifications for severe CDI per the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) include older age (>65), serious comorbidity, immunodeficiency and intensive care unit admission.[29]

Conclusions

This study provides valuable information to healthcare providers, hospital administrators, and policy makers regarding the demographics of hospitalised patients with CDI and CDI-associated patient mortality. Tuberculosis comorbidity should be considered a risk factor for CDI in addition to antibiotic use and prior healthcare exposure in populations with high tuberculosis and HIV comorbidity. Patients testing positive for *C. difficile* have a significantly higher and independent risk of mortality compared to patients with diarrhoea testing negative at public district hospitals in South Africa. These results can be used to identify patients at risk of developing CDI and to improve the quality of care provided to CDI patients in similar settings. Our results indicate improved CDI prevention, assessment, and management is urgently needed in the Western Cape Province.

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Contributors

LL designed the study, designed data collection, monitored data collection for the whole study, collected data, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. She is guarantor. SB provided guidance on the study and revised the paper. WR provided guidance on the study and revised the paper. NS provided guidance on the study and revised the paper. MB designed data collection tools, collected data, and revised the paper. RC facilitated the collaborative project between the University of the Western Cape and the University of Wisconsin, provided guidance on the study and revised the paper.

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the University of the Western Cape Department of Research Development, Ethics Reference Number: HS/16/1/24.

Data sharing: No additional data available. Statistical code available upon request.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have

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Table 1. Patient characteristics			
	Clostridium difficile (*C. difficile*) laboratory test result (PCR)		
Patient characteristic	**Positive (n=112)**	**Negative (n=138)**	**P-value**
Age average (years)*	47	40	<0.01
Sex (female)*	68%	63%	0.43
Documented HIV	71%	80%	0.07
CD4 < 200 cells/µl†	81%	81%	0.96
Documented tuberculosis	54%	32%	<0.001
Multi-drug resistant tuberculosis	9%	3%	0.04
Prior exposure to each *C. difficile* test	**Positive (n=112)**	**Negative (n=138)**	**P-value**
Hospitalised 30 days prior to admission	52%	22%	<0.001
Hospitalised 31-90 days prior to admission	44%	23%	0.001
30-day antibiotic exposure	83%	46%	<0.001
Penicillin	21%	11%	0.02
Quinolone	25%	10%	<0.01
Carbapenem	22%	4%	<0.001
Cephalosporin	50%	34%	<0.01
Clindamycin	4%	0%	0.03
31-90 day antibiotic exposure	29%	5%	<0.001
Penicillin	12%	1%	0.001
Quinolone	8%	1%	0.01
Carbapenem	2%	0%	0.12
Cephalosporin	13%	3%	<0.01
Clindamycin	0%	0%	

* Mean age and gender distribution calculated for 225 individual patients, excluding patients with more than one test (102 *C. difficile* +; 123 *C. difficile* -).
† Of HIV+ patients, patient CD4 counts were available for 178 *C. difficile* test results (74 *C. difficile* +; 104 *C. difficile* -).

Table 2. Univariate analysis of risk factors for mortality found to be marginally significant (P<0.1)	
Variables	**P value**
C. difficile test result	0.000
Hospitalised 30 days prior to admission	0.004
Critical care admission	0.014
Tuberculosis	0.046
Gender	0.051
Multidrug resistant tuberculosis	0.085
Hospitalised 90 days prior to admission	0.094
Hematochezia	0.097

Table 3. Logistic regression analysis of 30-day mortality				
Variable	**Odds Ratio**	**Std. Error**	**P value**	**95% Confidence Interval**
C. difficile test result	4.7	2.1	0.000	2.0 - 11.2
Hospitalised 30 days prior to admission	0.97	0.42	0.952	0.42 - 2.3
Hospitalised 90 days prior to admission	1.2	0.51	0.676	0.51 - 2.7
Critical care admission	13.8	17.9	0.044	1.0 - 176
Tuberculosis	2.3	0.91	0.038	1.0- 5.0
Gender	2.8	1.3	0.031	1.1 - 7.2
Multi-drug resistant tuberculosis	1	-	-	-
Hematochezia	0.14	0.15	0.069	0.02 - 1.2

Figure 1. Patient *Clostridium difficile* test result inclusion.

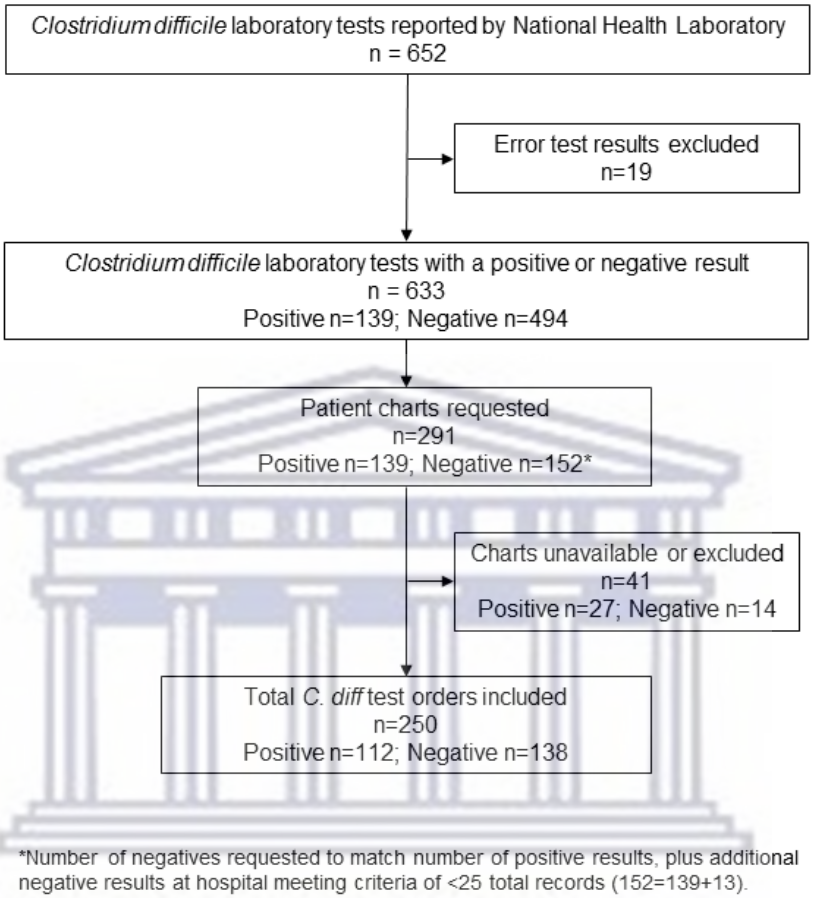
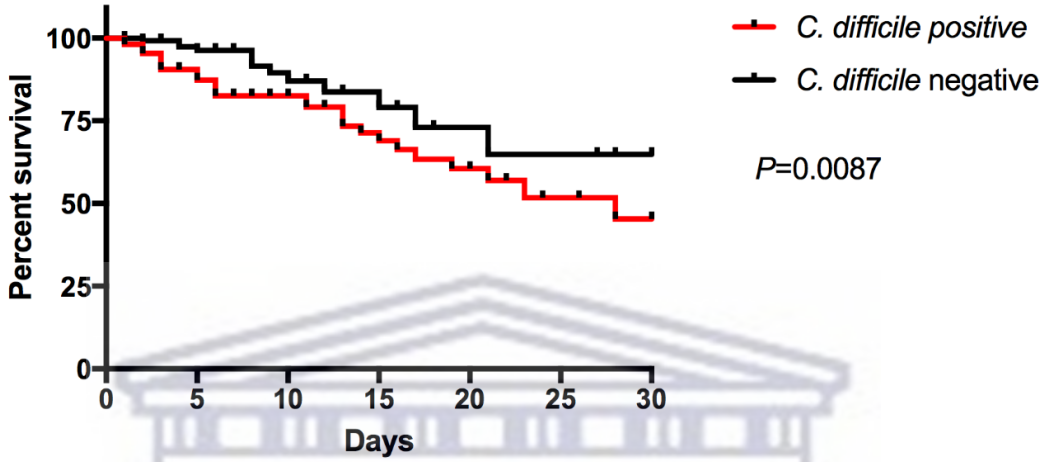


Figure 2. Survival curve for hospitalised patients with diarrhoea following a *Clostridium difficile* test. HR 2.0 (95% CI 1.1 to 3.6).



4.5 Contributions to the thesis

To the thesis, this publication and results chapter fulfils **Objective 1** to: determine the epidemiology, outcomes and management of patients with diarrhoea and tested for *C. difficile* infection in patients hospitalised at the district level in the Western Cape. The study also fulfils the sub-objectives to: 1a.) determine the risk factors for a *C. difficile* positive result compared with a *C. difficile* negative result; 1b.) determine the risk factors for mortality in South African patients in the Western Cape with diarrhoea. The results also identified opportunities for improvement in treatment provided and prevention measures (Objective 2b). In addition to the recommendations in the publication, we reported the study results and made recommendations to key stakeholders at the participating hospitals and the provincial Department of Health, addressing **Objective 4** (Report the findings regarding CDI in South Africa with recommendations for further research; Objective 4a: Report the findings regarding CDI epidemiology and outcomes with recommendations for further research).

4.6 Novel contributions to knowledge and implications

The results provide several original and significant contributions to knowledge. First, this study identified a novel risk factor for CDI. In this population with high tuberculosis and HIV comorbidity, tuberculosis was an additional risk factor. Second, despite standard treatment for CDI with most receiving metronidazole, mortality of patients with a *C. difficile* positive result was significantly higher than similar patients testing negative with diarrhoea (29% vs. 8%, $p<0.0001$). Third, the study contributed to the recommendation that vancomycin should be considered as an alternative to metronidazole in populations with high prevalence of tuberculosis and immunocompromising conditions given high mortality rates observed in this study and led to revision of the national Standard Treatment Guidelines for South Africa. The results underscore the need for improvements in quality of care and timely identification, treatment and IPC practices.

5 RESULTS: PERCEPTIONS AND PRACTICES

5.1 Reasoning

The reasoning for this paper was that healthcare provider CDI perceptions and practices in South Africa were unknown and necessary to develop appropriate education and interventions. An analysis of the barriers and facilitators to CDI identification and treatments was also necessary to develop interventions. Furthermore, CDI interventions must consider local context and perspectives of various levels of healthcare providers and stakeholders.

5.2 Publication attributes

This thesis chapter includes a reproduction of the study that has been published in *Antimicrobial Resistance and Infection Control* as:

Legenza L, Barnett S, Rose W, Emmerling T, Peh KH, Safdar N, Coetzee R. *Clostridium difficile* infection perceptions and practices in South Africa. Antimicrob Resist Infect Control. 2018;7:125. PMCID: PMC6206849

Like Chapter 4, reference citations from the publication are listed at the end of the manuscript in order of appearance.

The final PDF of the article is provided in thesis Appendix J, and author guidelines for *Antimicrobial Resistance & Infection Control* are provided in thesis Appendix K.

Antimicrobial Resistance and Infection Control is an accredited (DHET), peer-reviewed, and Medline indexed journal. Its 2020 JCR Journal Impact Factor is 4.887.

PubMed indexed articles cite this publication five times according to the NIH's iCite. Six documents in Scopus cite this publication, and five documents in Web of Science cite this publication. According to Google Scholar, the article is cited online ten times.

A study of CDI in Cameroon cited this paper when describing the persisting gap in CDI data from sub-Sahara Africa.[206] A 2020 qualitative systematic review of antimicrobial stewardship in sub-Sahara Africa describes the results of this thesis chapter, specifically CDI knowledge gaps, time limitations, and competing priorities for checking microbiology laboratory results.[207] A retrospective cohort study published in 2021 on CDI in the South African public sector cited this Results publication on how CDI is most commonly treated.[8] The International Society for Infectious Diseases' expert position paper on the CDI in hospitals also details the results on CDI knowledge gaps, lapses in following infection and prevention control practices, and how CDI outbreak experience supported CDI knowledge for some providers.[7] The significant CDI knowledge gaps identified are also cited in a 2022 review paper of CDI in Africa.[205]

5.3 Contributions

The candidate, Laurel Legenza was the primary contributing author and corresponding author of the study. Contributions to the paper are published as follows: "LL designed the study, designed data collection, monitored data collection for the whole study, conducted interviews, transcribed audio, analysed the data, drafted and revised the paper. SB provided guidance on the study and revised the paper. WR provided guidance on the study and revised the paper. NS provided guidance on the study and revised the paper. TE transcribed audio, analysed data, and revised the paper. KHP transcribe audio, analysed data, and revised the paper. RC facilitated the collaborative project between the University of the Western Cape and the University of Wisconsin, provided guidance on the study and revised the paper. All authors read and approved the final manuscript."

5.4 *Clostridium difficile* infection perceptions and practices in South Africa

Laurel Legenza

1. University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, Wisconsin 53705, United States

2. University of the Western Cape, Robert Sobukwe, Cape Town, 7535 South Africa

Legenza@wisc.edu

Susanne Barnett

1. University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, Wisconsin 53705, United States

susanne.barnett@wisc.edu

Warren Rose

1. University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, Wisconsin 53705, United States

warren.rose@wisc.edu

Nasia Safdar

3. University of Wisconsin School of Medicine and Public Health, 750 Highland Ave, Madison, Wisconsin 53726 United States

ns2@medicine.wisc.edu

Theresa Emmerling

1. University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, Wisconsin 53705, United States

emmerling@wisc.edu

Keng Hee Peh

1. University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, Wisconsin 53705, United States

peh2@wisc.edu

Renier Coetzee

2. University of the Western Cape, Robert Sobukwe, Cape Town, 7535 South Africa recoetzee@uwc.ac.za

Abstract

Background

Clostridium difficile infection (CDI) is understudied in limited resource settings. In addition, provider awareness of CDI as a prevalent threat is unknown. An assessment of current facilitators and barriers to CDI identification, management, and prevention is needed in limited resource settings to design and evaluate quality improvement strategies to effectively minimize the risk of CDI.

Methods

Our study aimed to identify CDI perceptions and practices among healthcare providers in South African secondary hospitals to identify facilitators and barriers to providing quality CDI care. Qualitative interviews (11 physicians, 11 nurses, 4 pharmacists,) and two focus groups (7 nurses, 3 pharmacists) were conducted at three district level hospitals in the Cape Town Metropole. Semi-structured interviews elicited provider perceived facilitators, barriers, and opportunities to improve clinical workflow from patient presentation through CDI (1) Identification, (2) Diagnosis, (3) Treatment, and (4) Prevention. In addition, a summary provider CDI knowledge score was calculated for each interviewee for seven components of CDI and management.

Results

Major barriers identified were knowledge gaps in characteristics of *C. difficile* identification, diagnosis, treatment, and prevention. The median overall CDI knowledge score (scale 0-7) from individual interviews was 3 [interquartile range 0.25, 4.75]. Delays in *C. difficile* testing workflow were identified. Participants perceived supplies for CDI management and prevention were usually available; however, hand hygiene and use of contact precautions was inconsistent.

Conclusions

Our analysis provides a detailed description of the facilitators and barriers to CDI workflow and can be utilized to design quality improvement interventions among limited resource settings.

Keywords:

Healthcare associated infection, Infection control, Qualitative study, antimicrobial stewardship, Global health

Background

Clostridium difficile infection (CDI) is an increasingly important healthcare-associated infection associated with long hospitalisations and high patient morbidity and mortality.[1] CDI often results from normal gut bacterial disruption due to broad-spectrum antimicrobial use, allowing for overgrowth of toxigenic *C. difficile*. CDI outbreaks have been reported extensively in the United States (US) and Europe over the last two decades. CDI in these hospitals is prevalent supporting extensive CDI prevention and control measures. However, CDI is understudied in low and limited resource settings, including nearly all African countries. Where limited data exists, a study at a tertiary hospital in Cape Town, South Africa found 22% of stool samples from patients with suspected CDI diarrhoea were *C. difficile* positive.[2] In addition, patients in South Africa are disproportionately affected by HIV and tuberculosis (TB) and therefore also experience known CDI risk factors of prior hospital and antibiotic exposure—exposures that can uniquely contribute to an increased risk of CDI and poor outcomes.[3 4]

Treatment of CDI requires a comprehensive approach that includes infection prevention and control (IPC) measures to limit transmission and prevent outbreaks. Although no CDI IPC guidelines exist specific to African countries, the Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases guidelines consistently recommend IPC components of antimicrobial stewardship programs (ASP) which include effective environment cleaning, patient isolation, use of personal protective equipment such as gowns and gloves, surveillance, and education.[5] These evidence-based recommendations are key to effective CDI management. The feasibility of using these recommendations in populations with limited healthcare resources has not been established. In addition, healthcare provider knowledge of CDI and the guidance to effectively mitigate and manage patient populations at higher risk for CDI is unknown.

Provider knowledge of CDI and treatment measures are essential to both successfully manage CDI and prevent disease transmission. An assessment of current facilitators and barriers to CDI identification, management, and prevention is needed to design and evaluate improvement strategies to effectively minimize the risk of CDI. To our knowledge, no comprehensive study of barriers and facilitators to CDI workflow (identification, diagnosis, treatment, and prevention) in Sub-Saharan Africa exists. Our study aims to fill this gap by eliciting CDI perceptions and management practices among healthcare providers in South African secondary hospitals to uncover facilitators and barriers to providing quality CDI care.

Methods

Data collection

We utilized a qualitative approach to elicit health care providers' perceptions of barriers and facilitators to CDI management because it provides detailed process oriented results. We conducted semi-structured interviews and focus groups among clinical providers at three secondary hospitals in South Africa. A Systems Engineering Initiative for Patient Safety (SEIPS) model served as a framework for the interview guide. The SEIPS framework connects work systems to patient and organizational outcomes, while including interactions in the work system between available tools, people, tasks, the internal environment, and the organization.[6] The semi-structured interview assessed each subject's CDI knowledge and traced workflow from patient presentation with CDI symptoms through CDI 1.) Identification, 2.) Diagnosis, 3.) Treatment, and 4.) Prevention. Interview questions were structured to reveal facilitators and barriers to these CDI workflow steps and opportunities to improve CDI treatment. The interview guide included optional probes to use when appropriate to gather additional information. When participants revealed a lack of CDI knowledge from the preliminary questions, the interview was then modified to contain general questions about diarrhoea management. The interview guide included optional probes to use when appropriate to gather additional information. When participants revealed a lack of CDI knowledge from

the preliminary questions, the interview was then modified to contain general questions about diarrhoea management. As a qualitative study, the interviewer could use information gathered from prior interviews to direct future interview discussions and build on emerging concepts. For example, asking for further detail and implications on processes mentioned with open-ended questions.

Participants

Providers working in three public secondary (district) level hospitals in the Western Cape, Cape Town Metropole, South Africa were invited to participate in this study. The three participating hospitals, averaging 265 inpatient beds overall, were previously selected to be included in a CDI quality improvement intervention. Our study aimed to interview, at minimum, 15 providers among five provider types including frontline nurses, nurse managers, pharmacists, junior physicians (registrars and medical officers), and senior physicians (consultants and department administrators). Semi-structured interviews and focus groups occurred August-November 2016.

Study investigators included healthcare providers from the US and South Africa with local hospital affiliations. The interviewers, a study investigator and a visiting US pharmacy resident, recruited front-line healthcare providers with convenience and snowball sampling, and recruited senior providers with purposive sampling. There were no participant exclusion criteria. Interviews were conducted as focus group discussions if preferred by participants. Participants were provided an informed consent document approved by the ethics committee prior to the interview and could decline participation at any time. Interviews were conducted by the interviewer in consultation rooms and offices. All interviews were conducted in English by one of the two interviewers with questions from a semi-structured interview guide and probing techniques by the interviewer. Interviews continued until thematic saturation was observed regarding barriers and facilitators for CDI treatment and management. The University of the Western Cape Research Ethics Committee granted approval for this qualitative study.

Data analysis

Interview audio recordings were transcribed verbatim and checked for accuracy. Data analysis included coding to factors determined a priori (including key workflow steps: 1) Identification, 2) Diagnosis, 3) Treatment, and 4) Prevention) as well as inductive coding to emerging themes.[7]. Two individuals from a team of three coders (LL, TE, and KP) conducted each coding phase. Paired coding with two coders per phase was performed to minimize bias. Coding schema was created to reconcile local medical terminology. Discrepancies in coding were resolved by consensus. Kappa scores were calculated to assess coding agreement at a mid-point and at the conclusion of coding. While we had initially planned to map results with the SEIPS framework, CDI management knowledge was significantly lower than expected and insufficient to frame the results in terms of tools, people, tasks, the internal environment, and the organization. Alternatively, we mapped coded themes to the workflow structure identified from the interviews.

After identifying large discrepancies in health care provider knowledge regarding CDI during the interview process, a scoring system was developed to categorize participants' CDI knowledge from their interview responses (Table 1). The intent of the assessment was to quantify the unexpected differences. With the knowledge assessment, one knowledge point was possible from each of the following seven CDI-related components: signs and symptoms (e.g. diarrhoea), characteristics of bacteria (e.g. microbiology, virulence mechanism, disruption of normal flora, opportunistic), hand hygiene (e.g. soap and water needed to clean hands, not just alcohol), treatment (e.g. metronidazole, oral vancomycin, fecal transplant, contraindication with loperamide), contact precautions/isolation (contagious), risk factors (e.g. healthcare exposure, antibiotic use, immunocompromised by medication or illness [cancer, HIV status, CD4 count <200] proton pump inhibitor use), and diagnosis (e.g. stool sample and testing methods, polymerase chain reaction[PCR]/toxin detection). The following responses did not receive a point allocation: 1) only stating 'bacterial infection' for characteristics of bacteria, 2)

stating a non-specific sign and symptoms of infection or illness without stating diarrhoea, 3) stating rehydration (electrolytes) without specific antibiotic treatment name. Total knowledge score from each individual interview was further classified into four categories: 'no knowledge' (0–1 point), 'limited knowledge' (2–3 points), 'moderate knowledge' (4–5 points), and 'advanced knowledge' (6–7 points). Each CDI knowledge category was also scored across all interviewees. Researchers conducted subgroup analysis of knowledge level based on occupation and performed analysis of individual CDI assessment knowledge categories by participant and occupation. The two focus group interviews were excluded from the knowledge assessment analysis due to potential knowledge score overestimation. However, dialogue from the group interviews was included in the qualitative analysis. All analyses were conducted using NVIVO software (Version 11, QSR International).

Results

A total of 26 semi-structured interviews were conducted with healthcare providers (11 nurses, 4 pharmacists, 11 physicians) of various rankings (Table 2). In addition, two focus groups were conducted; one with seven nurses and the second with three pharmacists, resulting in 36 study participants (Table 2). Kappa scores indicated high intercoder agreement (midpoint kappa = 0.71, final kappa 0.63). The median overall CDI knowledge score from the 26 individual interviews was 3 [interquartile range 0.25, 4.75]. Subgroup median knowledge scores and an analysis of responders' knowledge of each category are presented in Table 3. Inductive themes were coded for processes required for CDI workflow and organizational culture (beliefs and attitudes) regarding change (i.e. the ease of positive change at the organization or 'change culture') in order to inform future interventions. Healthcare provider responsibility and accountability for components of CDI management emerged as an organizational culture theme from the interviews. Thematic saturation of barriers and facilitators to CDI management was reached across the health care provider types (i.e. no additional themes emerged after iterative analysis of 26 interview and two focus group transcripts).[8] CDI workflow steps are presented

along with corresponding knowledge scores, barriers, and facilitators, (Section I: Workflow) and followed by organizational culture themes (Section II: Organizational Culture).

SECTION I: WORKFLOW

Figure 1 presents workflow depicted from interview results, along with facilitators and barriers to CDI management summarized in the context of the CDI workflow, including the previously identified steps of CDI identification, diagnosis, treatment, and prevention. When CDI is suspected, a stool sample is sent to an offsite laboratory for *C. difficile* identification by PCR. Following CDI diagnosis, treatment and infection prevention and control measures are initiated. Processes were consistent between healthcare providers with knowledge of the workflow step.

1. Identification and healthcare provider knowledge

CDI identification requires knowledge of the bacteria, risk factors and clinical suspicion when patients present with CDI signs and symptoms. A major barrier to identification is low CDI knowledge. Ten interviews (6 nurses, 4 pharmacists) scored as 'no CDI knowledge' (Table 3). One participant candidly revealed the lack of CDI knowledge.

"It's actually the first time that I hear about it, to be honest" - Pharmacist

CDI signs and symptoms were most commonly known by healthcare providers (n=16, 61.5%). Thirteen (50%) participants could not describe CDI risk factors that could prompt clinical inquiry for CDI; this knowledge gap creates a potential barrier for prompt identification. Two physicians reported extensive experience with CDI in the United Kingdom. A recurrent theme from the interviews among providers was that identification for HIV and TB was prioritized over CDI. Physicians who have worked in the United Kingdom (U.K.) elaborated that the sense of urgency in

South Africa for CDI was different than their previous experience due to competing attention of other prevalent disease.

When I was in the UK [United Kingdom] years ago… [when] the manager mentioned C. diff the staff would jump up and down and get incredibly panicky… we just don't have that sense of urgency here… if you mention to someone in any hospital, they will go 'Okay, what is that?' [in cavalier tone]... however, if you tell them there is a patient with a potential XDR-TB [Extensively drug-resistant TB], then they may jump up and down. So the whole thing with C. diff it's a reality… …a lot of people just think it's a disease with the elderly, but we have a lot of immunocompromised patients…" – Physician

At one hospital, CDI awareness in senior staff only increased after an outbreak in the hospital. Awareness was lower for rotating junior staff who did not experience the outbreak.

"In terms of my junior staff, I think [CDI] ranks quite low. I think it's got to do with the way we've become aware last year. We've had more cases making us aware that it's highly infectious." - Physician

While some providers conjectured CDI to be a national problem, others did not, and no providers were aware of CDI magnitude in South Africa. Facilitating CDI identification were the senior providers with higher CDI knowledge. At one of the hospitals, an ASP was referenced as attributing to low incidence.

2. Diagnosis

After identification, to inform diagnosis, a stool sample from the patient is tested at a laboratory for *C. difficile*. While all hospitals in our study had laboratory testing available to conduct a *C. difficile* PCR test, testing occurred offsite as there was not capacity for the PCR test at the onsite laboratory. In order to test for *C. difficile*, physicians must indicate the test on a standardized laboratory form. Perception of time to result varied widely and was attributed to delays in initiating treatment.

Additional barriers identified included staff difficulties obtaining stool samples due to staff shortages and non-standardized collection of laboratory samples. Laboratory test costs were occasionally cited as reasons to not test for *C. difficile*. Eleven interview participants described CDI diagnosis (42.3%, Table 3).

"Most of the time they are not tested, because they come from the emergency, and because our emergency is so busy, then the patient is pushed up to the ward. So then only when the patient is in the ward, and then we are actually reporting the [diarrhoea] to them [post call]. And then report that the patient is having diarrhoea; then that's the only time that they collect a stool specimen, and then after some, a couple of days, they get the results: the patient is positive. See... It could be about a week." - Nurse Focus Group

Other attributes identified in delaying the time to diagnosis include waiting for a physician to suggest the *C. difficile* test or until ward rounds to order it. To find results, physicians must proactively login to the database—usually from their personal mobile phones, as computer stations are not easily available. One of three hospitals uses a mobile messaging application for direct messaging from the microbiology laboratory to physicians with the goal of reducing the result notification time.

"I think the one resource that we've shown very well is the communication system. I think we chose the cheapest one we could find which is WhatsApp and that does make a difference in terms of managing your patients and getting a quicker diagnosis. The thing about WhatsApp is if a patient had a positive result, it would take the doctor another two days to figure it out that an infection exist. We actually have an alert system that works." - Physician

After observing the test result, the physician informs the nursing staff if the patient has a CDI. The IPC nurses are also informed of results and may, in turn, inform the medical team. However, there is not a timely and consistent pathway for this

notification, especially during post-call hours. The IPC nurse sends physicians a report including positive *C. difficile* test results on a monthly basis.

3. Treatment

Antibiotic treatment options for antibiotic-associated diarrhoea included in South African treatment guidelines at the time of the interviews were oral metronidazole initially and oral vancomycin for diarrhoea not responsive to metronidazole; vancomycin must be oral to reach the infection. Of note, the interviews were conducted prior to the revised IDSA CDI guidelines in 2018.[3] Eight (30.8%) respondents mentioned CDI treatment options, including treatment with metronidazole and vancomycin, though the importance of antibiotic treatment administered orally was reported inconsistently and occasionally inaccurately.

A few providers also discussed the clinical use of metronidazole compared to vancomycin, including patients' illness severity.

"So patients who don't respond to metronidazole would definitely be candidates for vancomycin or a metronidazole allergy." – Physician

Communication barriers were attributed to delays in treatment and included factors such as results being finalized while the physician was post call and drug order errors needing clarification.

Healthcare providers' high familiarity with metronidazole and its availability on the hospital floor as ward stock facilitated its use for CDI treatment. To order vancomycin and other antibiotics on the Essential Medicine List for Hospital Level Adults, providers needed to complete a pharmacy-approved motivation form that facilitates appropriate antibiotic use. Participants reported a time gap between ordering, sending the medication chart to the pharmacy, having the medication delivered to the ward, and administrating it to the patients. Some orders might be written up and not sent to the pharmacy. For stat orders, nurses may retrieve orders from the pharmacy. The pharmacies were closed during evenings and weekends.

An emergency stock of inventory is kept in the emergency center. If the needed drug is unavailable, an on-call pharmacist is called-in to prepare it. Occasionally medication was not administered and incorrectly documented as unavailable while drug was available in the emergency stock. Other reported barriers to patients receiving medications as ordered included: illegible handwriting, medication orders not including which ward an order came from, and physicians writing brand names when nurses only know the generic name. Additionally, sometimes a medication was given and not recorded; other times the patients missed doses because they were not present.

"The problem with this is...that sometime the results come back, the doctor is post call. Yes, and then he will only get the feedback the next day when he is actually coming to check on his patients. So that is the delay to start"- Nurse Focus Group

4. Prevention: contact precautions, hand hygiene, isolation, environmental cleaning

Contact precautions

CDI prevention procedures include contact precautions (e.g. gown, gloves) to reduce the risk of *C. difficile* spreading to other patients. Twelve (46.2%) participants reported the need for strict contact precautions when CDI was suspected or diagnosed. Supplies and procedures for IPC (included posters displaying orders for contact precautions) were usually available but not always utilised. Supplies (including gowns, gloves, masks, and hand sanitizer) were available in close proximity to a patient once contact precautions were ordered. Staff education and timely notification of need for infection control were the most common barriers to IPC measures. Pressure from patient bed shortages can lead to patients being placed near each other. Contact precautions with the first suspicion of CDI was described at one of the hospitals.

"...any patient with diarrhoea is placed with contact precaution; until we know if they have been exposed to any antibiotics, we put them as high risk." - Physician

At the three hospitals, the ward nurse in charge will enforce contact precautions with the nurses and the attending/consulting physicians will enforce junior physicians' contact precautions. The IPC team also enforces IPC practices. Both physicians and nurses inform patients about contact precautions; patients are told to inform their family members. While senior physicians reported informing patients of the need for IPC in the CDI setting, nurses considered themselves more approachable than the physicians and took a primary role in communicating with patients. One junior physician admitted his/her peers' shortfalling.

"I think that from all of it, that is where the biggest failing comes in—that we often don't tell patients enough of the stuff. So, I would like to think that once it's done there is a proper [communication] about the patient having things that can be transmitted, with words that they can understand and the importance of them not going around and touching lots of things and letting them know the reasons for gloving up and putting on gowns and stuff for their own peace of mind…It's apathy from the medical staff we forget to do these things..." – Physician

Hand hygiene

Facilitators and barriers to hand hygiene were related to the treatment of patients with CDI and additional infections. Hand hygiene practices for patients with CDI should include hand washing with soap and water to remove *C. difficile* spores that are not killed by alcohol hand sanitizers. Supplies, including paper towels, soap, and hand sanitizer, were frequently available but not always utilised. Some stated that insufficient supplies were a barrier; others said that supplies were always available. Eleven (42.3%) participants acknowledged the importance of washing hands with soap and water when treating patients with CDI (Table 3).

"...have to use soap and water, we take [the] de-germ [alcohol based hand sanitizer] away from bedside so they are forced to use soap and water." - Physician

Some perceptions regarding this important hand hygiene practice were inaccurate.

"I would not say a normal hand soap is better for C. diff*, I would say something alcohol based."* - Physician

Staffing shortages and high workload were described as reasons for inconsistent hand hygiene practices.

"Can I tell you, all over the basins is that sign [WHO's "5 Moments of Hand Hygiene"]... but we don't practice it...We don't follow five moments of Hand Hygiene. We follow it when we go home... You can't afford to take that five minutes." – Nurse Focus Group

Participants described hand hygiene events (e.g. ultraviolent light, blue soap) in their hospitals that encouraged effective hand hygiene. Many stated that overcrowding and lack of facilities (e.g. one sink per ward) hindered hand hygiene as well as: the high ratio of patients to nurses, education limitations, and sometimes-empty alcohol and/or soap dispensers.

Isolation

Infrastructure limitations were a major barrier to IPC, often preventing CDI patients from allocation to an isolation room. Isolation room availability ranged from two to four rooms. Isolation rooms were specifically prioritized for multidrug resistant tuberculosis (MDR-TB) patients, who may occupy the room for a month. CDI is viewed as a lower priority for isolation rooms.

"The fact that we have got a lot of immunocompromised patients in terms of our HIV rates and TB rates, a lot of our patients are at risk due to the use of antibiotics.

In the UK we used to see a lot of elderly patients, but here you have got a different spectrum of patients, so C. diff is a huge risk… I think everyone focuses on MDR and very few people actually focus on C. diff … C. diff is not something that is high on the radar." – Physician

Challenges for IPC included patient education regarding IPC, especially patients leaving isolation, walking around the hospital, and using shared bathrooms.

"The big problem that we have in our wards is a lack of isolation facilities. For an entire hospital, we've got only four isolation rooms [that] do not include isolation bathrooms. So a C. diff patient would have to use the same toilet as other patients." - Physician

Both nurses and physicians described speaking to patients and their family members about isolation. An elevated desire from patients to understand their condition was expressed when patients were moved to an isolation room.

"Sometimes you'll find the patient doesn't know what is going on, but when you move them into an isolation room then they want to know why." - Nurse

Environmental Cleaning

The ward managers inform cleaning staff verbally about room cleaning needs. Under supervision, the cleaners complete a written checklist for the bathrooms and patient rooms. Cleaning is sometimes rushed due to high bed demand, and the staff nurses will help.

"It's just that we are busy so the beds are always in demand so sometimes there is no opportunity for cleaning because everything is rush, rush, rush, rush. When the patient is waiting on discharge, others are waiting for that bed so we don't have the opportunity to do the spring cleaning of the unit. We aren't always able to do it in a calm environment." – Nurse

SECTION II: ORGANIZATIONAL CULTURE

Themes related to organizational culture (beliefs and attitudes) and how leadership and administration respond to new ideas, specifically 'change culture', were analyzed in order to inform future interventions. Through this coding an additional organizational culture theme emerged related to healthcare provider responsibility and accountability.

Change culture: how leadership and administration respond to new ideas

The majority of respondents described leadership as being supportive of new ideas. Some respondents did not feel leadership was supportive of bottom-up ideas; others believed that ideas with evidence of positive impact would be supported. A few respondents noted a barrier to change related more to nursing staff and junior physician turnover than to administrative support. Progressive change is difficult when the same education concepts are repeated with rotating healthcare providers; institutional memory regarding CDI and CDI management was lost.

"*Implementing change and practical change are very different, so we are able to change our practice so we can make lots of suggestions... but the difficulty comes in that our staff [is a] rotating staff*." - Physician

A nurse new to a leadership position anticipated facing challenges in changing long-standing practices.

"The people above me, the specialist physicians or consultants, are quite open to change. If you can show clearly that an idea is going to work, the department is open to change and improving things. As you get higher up the leadership chain, it becomes more difficult to introduce change. I do find that on the face of it, the managers seem to be okay and accepting and are happy to listen." - Physician

Responsibility and accountability

While the interviewees described achievements of and challenges for patients and healthcare providers following IPC precautions, low adherence emerged as a compelling theme—sometimes in the context of IPC in general and for the treatment of TB, particularly when participants had limited CDI knowledge. Perception of the threats from infectious diseases and IPC prioritization also appear to be barriers to adherence when supplies are available. Accountability structures are not in place to properly encourage providers to remain knowledgeable about guidelines nor enforce IPC precautions.

"It seems we have many awareness days… we had spike last year, two years ago… we have had quite a few staff members contracted tuberculosis… people only get aware if their buddy gets it… It makes it real." – Physician

"Just to get the doctors to wear gloves—that for me is another thing where I can just say… like, 'Why are you not wearing gloves?' or, just tell them 'Your patient has TB. Can you put on your mask please?'...together with the hand washing, and at the end of the day, it is part of the IPC principles to have full personal protection equipment available in the unit, but there's hand sanitizers, soap, and water, available in the unit, so no one has an excuse." – Physician

Informal structures for peer accountability were discussed as a helpful strategy from two interviews. First, accountability for hand hygiene occurred on the ASP ward round at one hospital. Second, an Operational Manager in the Operating Room (Theater) described nursing and cleaning staff who speak up about needs and follow cleaning expectations.

"The cleaning staff and the nursing staff is quite well informed as to what is supposed to happen, because sometimes they can tell you. 'Sister, this was not done yet; You can't really put your patient here'… Those are the people that I work with... that I come across, that will tell me. Doesn't matter if you are the cleaner,

you can tell me, 'Sister, it's not ready yet.' You understand. It's that relationship that we have [of a] multidisciplinary team, to do what is expected of us." – Nurse

Discussion

Principal findings

This is the first qualitative study of CDI in Sub-Saharan Africa, and the results provide novel insight into CDI treatment and workflow in a limited resource setting. The context of CDI in Africa is especially important to consider given the high HIV and tuberculosis prevalence and high risk of *C. difficile* associated mortality in this population. This study reveals significant barriers and facilitators to CDI treatment in public district (secondary) level South African hospitals. Major barriers included knowledge gaps in CDI management, especially regarding awareness of the infection, transmission, treatment, and IPC practices among health care providers. Physician CDI knowledge was higher than nurse and pharmacist knowledge. The results reveal opportunities for healthcare provider education related to CDI. Our study affirms that healthcare providers have an awareness of evidence-based IPC precautions but barriers to following them include perceptions of priority and time availability.

Implications: perceptions and knowledge

Based on quantitative results from the overall CDI knowledge assessment, participants had limited CDI knowledge. Gaps in CDI knowledge may delay clinical suspicion and all workflow steps in CDI identification, diagnosis, treatment and prevention. While physicians scored higher, some physicians were less confident regarding when to order the *C. difficile* test resulting in delayed diagnosis. Physicians with high CDI knowledge noted an urgency surrounding CDI not observed in junior physicians and other healthcare providers. This, together with a high risk of mortality in patients with positive *C. difficile* test results, underscores

an urgent need for education and intervention tailored to relevant aspects of healthcare providers' job responsibilities.

Overall, participants scored well in areas of identifying CDI risk factors, signs, and symptoms. However, improvement is needed in terms of educating healthcare professionals in South Africa about other aspects of CDI. In the occupation subgroup analysis, nurses and pharmacists appear to be less knowledgeable about CDI characteristics, with response rates of 50% or less in all the knowledge assessment categories. The identified areas for potential development relevant to nurses and pharmacists are: CDI patients' need for contact isolation, the importance of hand washing instead of using alcohol gel in preventing the spread of CDI, and CDI treatment options. Nurses can also be educated to suspect CDI when monitoring bowel movements.

This study reveals a more complicated process for obtaining and administering vancomycin compared to metronidazole that may be hindering healthcare providers' use of vancomycin. In an epidemiology, treatment, and outcomes study in the same setting, vancomycin was rarely ordered (2%) as initial CDI treatment.[4] One strategy is to incorporate treatment options for CDI into pharmacist education and teach pharmacists what to look for on physician-submitted motivation forms. Pharmacist education about treatment options is especially important considering the role pharmacists have in the approval process for vancomycin use. The healthcare team should be educated on the clinical use of vancomycin for CDI with an emphasis on timely preparation and delivery.

How results relate to other studies

Our study affirms current literature's described need for improved CDI identification in settings with extensive CDI experience. Despite a history of substantial CDI outbreaks in Europe, a study identified persistent underdiagnoses of CDI when all diarrhoea samples were tested at 482 hospitals across 20 European countries; 23% of *C. difficile* positive results were not identified at the local

hospital. Authors attributed the underdiagnoses to a lack of clinical suspicion and suboptimal laboratory diagnostic methods.[9] Meanwhile, in the US, a regulatory climate that reduces hospital reimbursement for patients who develop hospital-acquired infections is driving efforts to refine testing protocols to avoid *C. difficile* over testing and inappropriate diagnosis.[10] These studies emphasize the importance of appropriate testing for diagnosis.

A global review of CDI guidelines found antimicrobial stewardship (ASPs) to be universally recognized as an essential evidence-based component of CDI IPC.[5] Continued development of interdisciplinary ASPs in limited resource settings is necessary to facilitate effective CDI management and IPC measures.

One barrier to hand hygiene identified in this study was the perception that there is insufficient time available for thorough hand cleaning. Indeed, in a study conducted in the US about healthcare providers' compliance with IPC practices for patients with CDI, full compliance was very low and time-consuming with a mean time for full compliance greater than five minutes for patients in single isolation rooms.[11] Patient care workload continues to be a barrier to full compliance with CDI contact precautions in high resource settings.[12] Therefore, improving full compliance of IPC practices in limited resource settings will require both a workload adjustment to allow more time per patient and education on the importance of CDI-related IPC practices.

Significant challenges for the implementation of IPC programs and practices exist in low and limited resource settings, including infrastructural constraints with a limited number of isolation rooms and variable staff compliance with hand hygiene practices. A similar qualitative study in India found perceived workload and nursing staff turnover to be barriers to infection control.[13] This relates to our study's previously referenced finding that perceived workload hindered infection control practices, especially regarding hand hygiene. Our respondents reported high turnover of both nursing staff and junior physicians as barriers to implementing change. The secondary hospitals included in our study did not have an IPC team as

developed as the one in the tertiary hospital in India. The study in India also found participants reporting the availability of IPC supplies but experiencing challenges with compliance, while an international study of healthcare settings representing 30 countries identified inadequate supplies as a barrier to infection control of multidrug resistant organisms in some high and middle income countries.[13 14]

Limitations

As a qualitative study, the results are not generalizable to a larger population but may be transferable to similar settings. Visiting researchers' presence conducting the interviews may have affected responses; stated practices are not necessarily the reality of practice. While all interviews were conducted in English, English was a second language for some participants. This may have limited the respondents' understanding of some questions and ability to articulate responses. Furthermore, we may have underestimated facilitators to CDI management in an attempt to identify improvement opportunities. Our analysis was not a systematic audit of workflow and practices, and some inaccuracies may exist. To mitigate bias, multiple researchers of the study team reviewed the results. Finally, as we developed the knowledge assessment after the interviews were completed, the assessment is not yet validated and results are limited. Our knowledge assessment measured breadth of CDI knowledge and not depth. For example, some providers gave detailed explanations for some of the knowledge components, such as advantages of different testing protocols, yet these explanations were still only assigned one point for that component.

Conclusions

Our analysis provides a detailed description of the facilitators and barriers to CDI workflow, including the need for increased healthcare provider knowledge of CDI management. Interventions should increase CDI knowledge and utilization of the available systems and supplies by addressing the identified barriers and championing the identified facilitators. Increasing CDI knowledge alone is unlikely

to be effective without addressing the need to create a sense of urgency around CDI and appropriate IPC practices. The results provide context for technical intervention and implementation strategies in low-resource public healthcare settings. This study serves as a baseline and supplements quantitative CDI patient data from ongoing CDI research including provider education and a clinical intervention to improve CDI quality of care in South Africa. The results of this workflow and provider knowledge analysis identify areas of need and are useful to design interventions to improve the quality of care for CDI patients in this population and similar limited resource settings.

Abbreviations

ASP: Antimicrobial stewardship programs
CDI: *Clostridium difficile* infection
IPC: Infection prevention and control
MDR(-TB): multidrug resistant(-tuberculosis)
PCR: Polymerase chain reaction
SEIPS: Systems Engineering Initiative for Patient Safety
TB: Tuberculosis
UK: United Kingdom
US: United States
XDR-TB: Extensively drug-resistant TB

Declarations

Ethics approval and consent to participate

The study was approved by the University of the Western Cape Department of Research Development, Ethics Reference Number: HS/16/1/24. Participants were provided an informed consent document approved by the ethics committee prior to the interview and could decline participation at any time.

Consent for publication

Not applicable.

Availability of data and material

De-identified interview transcripts are available on request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LL designed the study, designed data collection, monitored data collection for the whole study, conducted interviews, transcribed audio, analysed the data, drafted and revised the paper. SB provided guidance on the study and revised the paper. WR provided guidance on the study and revised the paper. NS provided guidance on the study and revised the paper. TE transcribed audio, analysed data, and revised the paper. KP transcribe audio, analysed data, and revised the paper. RC facilitated the collaborative project between the University of the Western Cape and the University of Wisconsin, provided guidance on the study and revised the paper. All authors read and approved the final manuscript.

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Table 1. *Clostridium difficile* knowledge assessment

Criteria for *Clostridium difficile* knowledge	**Points**
Signs and symptoms (diarrhoea)	1
States characteristics of bacteria (any mention of: microbiology, virulence mechanism, disruption of normal flora, opportunistic)	1
Soap and water needed to clean hands, not just alcohol	1
Treatment options (any mention of: metronidazole, oral vancomycin, fecal transplant, contraindication with loperamide)	1
Contact isolation needed (or contagious)	1
Risk factors (immunocompromised, antibiotic use, proton pump inhibitors)	1
Diagnosis (stool sample, testing methods [PCR/toxins])	1
Total points	=
No knowledge = 0 – 1* **Limited knowledge** = 2 – 3 **Moderate knowledge** = 4 – 5 **Advanced knowledge** = 6 – 7 * point allocation of 1 is considered no knowledge because there are multiple diseases associated with any one of the criteria, unless person states characteristics of bacteria	

Table 2. Occupations and stated titles of healthcare providers interviewed

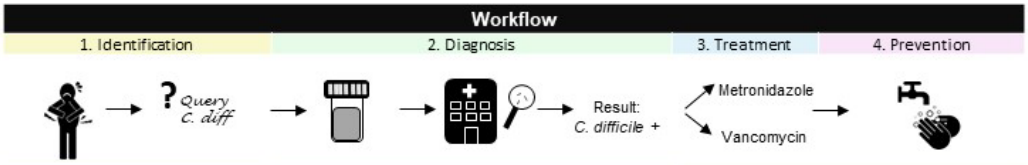
Healthcare Provider Occupation	**Participants**	**Interviews**
NURSE		
Operational managers or Assistant manager	4	4
Registered nurse or unspecified nurse	4	4
Infection Prevention and Control Nurse	2	2
Nurse Training Clinical Program Coordinator	1	1
Ward Nurses Focus Group Interview	7	1
Subtotal:	**18**	**12**
PHARMACIST		
Pharmacist	4	4
Pharmacist Focus Group Interview	3	1
Subtotal:	**7**	**5**
PHYSICIAN		
Head of Department	2	2
Consultant	1	1
Unspecified physician	1	1
Registrar	1	1
Medical officer	5	5
Intern	1	1
Subtotal:	**11**	**11**
TOTAL (N)	**36**	**28**

Table 3. *Clostridium difficile* infection (CDI) knowledge scores overall, by healthcare provider, and each CDI knowledge category

CDI knowledge sorted by healthcare provider					
		Occupation			**Overall**
		Nurse (n=11)	Physician (n=11)	Pharmacist (n=4)	All participants (n=26)
Median Score (0-7), [1st, 3rd interquartile]		1 [0, 2.5]	5 [4, 6]	0.5 [0, 1]	3 [0.25, 4.75]
Knowledge Classification, n (%)					
No		6 (54.5)	0 (0.0)	4 (100.0)	10 (38.5)
Limited		4 (36.4)	0 (0.0)	0 (0.0)	4 (15.4)
Moderate		0 (0.0)	6 (54.5)	0 (0.0)	6 (23.1)
Advanced		1 (100.0)	5 (45.5)	0 (0.0)	6 (23.1)
Knowledge assessed in each CDI knowledge category					
Components of CDI knowledge assessment, n (%)					
1. Identification	1.1 Characteristics of bacteria	2 (18.2)	4 (36.4)	0 (0.0)	6 (23.1)
	1.2 Risk factors	3 (27.3)	10 (90.9)	0 (0.0)	13 (50.0)
	1.3 Signs and symptoms	3 (27.3)	11 (100.0)	2 (50.0)	16 (61.5)
2. Diagnosis	2.1 Diagnosis	1 (9.1)	10 (90.9)	0 (0.0)	11 (42.3)
3. Treatment	3.1 Treatment options	1 (9.1)	7 (63.6)	0 (0.0)	8 (30.8)

4. Prevention	4.1 Hand washing needed	4 (36.4)	7 (63.6)	0 (0.0)	11 (42.3)
	4.2 Need for contact isolation	4 (36.4)	8 (72.7)	0 (0.0)	12 (46.2)

Figure 1. *Clostridium difficile* infection (CDI) identification, diagnosis, treatment, and prevention workflow: facilitators and barriers



1. Identification	2. Diagnosis	3. Treatment	4. Prevention
• Patient's presentation with CDI symptoms, including diarrhea and history of CDI risk factors. • Provider suspects CDI.	• Physician orders stool sample. C. difficile test must be indicated on the standardized laboratory form. • Sample collected by nurse. • Sample sent to offsite microbiology laboratory at tertiary hospital for testing. • Physician must log-in to database to find result. • Physician reviews result and patient status.	• Physician orders antibiotic treatment. • Vancomycin requires motivation form submitted to the pharmacy. • Contact precautions (gown, gloves, hand washing) ordered, if not already ordered. • Isolation room requested.	
Knowledge Assessment Category			
1.1 Characteristics of bacteria 1.2 Risk factors 1.3 Signs and symptoms	2.1 Diagnosis	3.1 Treatment options	4.1 Hand hygiene 4.2 Contact precautions and isolation
Barriers			
• Most healthcare providers had limitations in knowledge of CDI symptoms and risk factors. • HIV and TB higher priority for identification than CDI.	• Junior physicians may wait until ward rounds to order test. • Difficulties obtaining stool sample. • Cost considerations. • Test result may be delayed from offsite transportation. • Variable perceptions on time to result (<24 hours - 2 days). • Physician notification of laboratory result not automated.	• The importance of antibiotic treatment orally administered was inconsistent and occasionally inaccurate. • Use of metronidazole compared to vancomycin based on clinical severity was also variable. • Time gaps in ordering test and viewing result may delay treatment. • Very few isolation rooms for size of the hospital. Isolation rooms prioritized for MDR-TB patients. • Lack of facilities, for example one sink per ward, hindered hand hygiene. • Provider use of available supplies was described as inconsistent. • Providers did not perceive they had enough time for proper hand hygiene due to high patient care workload.	
Facilitators			
• A few providers had extensive knowledge and experience treating CDI.	• Laboratory testing available. • A database with the microbiology test result is available. • At one of three hospitals a mobile messaging application is used for direct messaging from microbiology laboratory to physicians with final result.	• Metronidazole available as ward stock. • Infection Prevention and Control (IPC) supplies are usually available, and near patient, gown and gloves. • Posters for contact precautions are posted with orders. • Both nurses and physicians described speaking to both the patient and their family about CDI and need for IPC measures. • Environmental cleaning staff clean patient areas daily.	

5.5 Contributions to the thesis

To the thesis this study fulfills **Objective 2** to: identify CDI perceptions and management practices among healthcare providers in South African secondary hospitals and uncover facilitators and barriers to providing quality CDI care. In this chapter we analyzed interview data with qualitative thematic analysis to uncover these facilitators and barriers (Objective 2a). In addition to the publication and included recommendations, we reported the study results and made recommendations to key stakeholders at the participating hospitals and the provincial Department of Health, addressing **Objective 4** (Objective 4b).

5.6 Novel contributions to knowledge and implications

The results provide novel insights on how CDI is identified and managed in South Africa, along with facilitators and barriers to care. The qualitative approach to this study allows for a detailed description of the facilitators and barriers to CDI workflow. The practical results can be utilized to design quality improvement interventions among limited resource settings where available supplies and healthcare provider training is similar to public South African hospitals. Major barriers identified were substantial knowledge gaps in characteristics of CDI identification, diagnosis, treatment, and prevention, including many providers who had no knowledge or were unaware of the infection characteristics. Thus, CDI interventions must include components of education tailored to the knowledge of the healthcare provider.

6 RESULTS: INTERVENTION AND IMPLEMENTATION

6.1 Reasoning

Our quantitative and qualitative research identified gaps in CDI knowledge and treatment measures provided. This paper describes the development of our context-informed CDI intervention and analyzes the CDI intervention and implementation process with implementation science frameworks. Implementation strategies are detailed with ERIC. The CFIR and FRAME-IS frameworks were applied to collected data and observations to identify drivers and barriers to implementation and understand differences in uptake. The reasoning for using an implementation science lens in this paper is that the results could support sustainability and scalability of future CDI intervention implementations.

6.2 Publication attributes

This thesis chapter includes a reproduction of the manuscript that has been accepted for publication in *Research in Social and Administrative Pharmacy*:

Legenza L, Coetzee R, Rose WE, Esack-Smart T, Crombie C, Mina M, Safdar N, Barnett SG. Application of Consolidated Framework for Implementation Research to improve *Clostridioides difficile* infection management in district hospitals. *Research in Social and Administrative Pharmacy*. 2022. Accepted for publication.

Like Chapters 4 and 5, the in-text reference citations in the manuscripts continue are listed at the end of the manuscript, numbered in order of appearance.

The PDF of the published article is provided in thesis Appendix L, and author guidelines for Research in Social and Administrative Pharmacy are provided in thesis Appendix M.

The appendix from this accepted manuscript provided with the thesis appendices (Appendix N) and includes supplemental detail on training adaptations and CFIR constructs. Supplement specific references are also listed at the end of this supplement.

Research in Social and Administrative Pharmacy is a peer-reviewed, DHET accredited in South Africa, and Medline indexed journal. Its 2020 JCR Journal Impact Factor is 3.336.

6.3 Contributions

The candidate, Laurel Legenza was the primary contributing author and corresponding author of the study. Contributions to the paper are included in the publication as follows:

"Laurel Legenza: Conceptualization, Project administration, Methodology, Investigation, Formal analysis, Data Curation, Writing - Original Draft, Writing - Review & Editing. Renier Coetzee: Conceptualization, Project administration, Methodology, Formal analysis, Writing - Review & Editing, Supervision. Warren E. Rose: Conceptualization, Methodology, Writing - Review & Editing, Supervision. Tasneem Esack: Formal analysis, Writing - Review & Editing. Kenneth Crombie: Investigation, Formal analysis, Writing - Review & Editing. Megan Mina: Investigation, Formal analysis, Writing - Review & Editing. Nasia Safdar: Conceptualization, Methodology, Writing - Review & Editing, Supervision. Susanne G. Barnett: Conceptualization, Methodology, Writing - Review & Editing, Supervision."

6.4 Application of consolidated framework for implementation research to improve *Clostridioides difficile* infection management in district hospitals

Abstract

Background:

Clostridioides difficile infection (CDI) contributes the global threats of drug resistant infections, healthcare acquired infections and antimicrobial resistance. Yet CDI knowledge among healthcare providers in low-resource settings is limited and CDI testing, treatment, and infection prevention measures are often delayed.

Objectives: to develop a CDI intervention informed by the local context within South African public district level hospitals, and analyze the CDI intervention and implementation process.

Methods:

A CDI checklist intervention was designed and implemented at three district level hospitals in the Western Cape, South Africa that volunteered to participate. Data collection included a retrospective medical records review of patients hospitalized with *C. difficile* test orders during the 90 days post-implementation. Patient outcomes and checklist components (e.g. antibiotics) were collected. Qualitative interviews (n=14) and focus groups (n=6) were conducted with healthcare providers on-site. The Consolidated Framework for Implementation Research (CFIR) and the Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies (FRAME-IS) were applied to collected data and observations in order to identify drivers and barriers to implementation and understand differences in uptake.

Results:

One of the three hospitals displayed high intervention uptake. Highly relevant CFIR constructs linked to intervention uptake included tension for change, strong peer intervention champions, champions in influential leadership positions, and the intervention's simplicity (CFIR construct: complexity). Tension for change, a recognized need to improve CDI identification and treatment, at the high uptake

hospital was also supported by an academic partnership for antimicrobial stewardship.

Conclusions:

This research provides a straight-forward health systems strengthening intervention for CDI that is both needed and uncomplicated, in an understudied low resource setting. Intervention uptake was highest in the hospital with tension for change, influential champions, and existing academic partnerships. Implementation in settings with fewer academic connections requires further testing of collaborative implementation strategies and proactive adaptations.

Keywords

Clostridioides difficile infection, Healthcare associated infection, Antimicrobial stewardship, District level hospital, Implementation Science, Global Health

Introduction

Patients with *Clostridioides difficile* infection (CDI), can suffer from health outcomes that range from mild-to-severe diarrhoea to mortality, as well as experience costly hospitalizations and readmissions.[1-6] In addition to physical impacts, CDI impairs patients' psychological, social, professional, and financial lives.[7 8] CDI remains a global health threat with incidence in South Africa similar to Europe.[4 5 9-11] CDI hospital outbreaks may trigger changes in patient care protocols including closure of hospital wards to limit further transmission.[12-14] Quality CDI care requires timely identification, rehydration, antibiotic treatment, and use of infection prevention and control (IPC) measures to prevent devastating hospital outbreaks.[5 15 16] Measurable gaps exist in the delivery of these steps as well as CDI knowledge across healthcare providers in hospitals in the Western Cape, South Africa, and likely in similar low-resource settings.[17 18] CDI interventions developed and proven in high resource settings, where most CDI epidemiological and quality improvement studies are performed, may not apply directly to low resource settings.[9 19] There is a gap in CDI literature from low resource settings,

especially sub-Saharan Africa, particularly in adapting CDI interventions to low resource settings.[9 20 21] Authors of a recent meta-analysis of CDI in developing countries concluded CDI prevalence in patients with diarrhoea (15%) is likely an underestimate due to inconsistent diagnostics, surveillance, and low awareness.[20] Thus, CDI interventions and the description for their implementation tailored to these local circumstances are urgently needed.

Implementation Science is a multidisciplinary research field and often aims to improve healthcare systems by optimizing the fit of evidence-based practices and interventions with implementation context.[22 23] It also aims to increase intervention reproducibility and transferability, and reduce the lag time between evidence generation and practice.[22-25] Yet, pharmacy has not fully integrated Implementation Science frameworks and strategies to enhance pharmacist-led interventions.[26 27] The Consolidated Framework for Implementation Research (CFIR) is a highly cited and adaptable meta-theoretical framework that excels in examining the interplay of contextual factors surrounding an intervention.[28] CFIR organizes theory and evidence-based constructs into five domains with a total of 39 constructs.[28] However, Implementation Science applications are lagging in low- and middle-income countries (LMICs).[29-31] Limited CFIR applications have been done in sub-Saharan Africa, primarily via academic partnerships in Kenya, Mozambique, and South Africa.[31-34] No prior work to our knowledge has leveraged implementation science to develop and explain a CDI intervention in South Africa.

The first objective of this study is to develop a locally-informed CDI intervention within South African public district level hospitals following implementation science principles. The second objective is to analyze the development of the CDI intervention, implementation process and implementation adaptations to understand differences in acceptance and uptake of the CDI intervention.[28 35] The study objectives were achieved; the methods describe steps for developing the intervention and conducting the CFIR analysis. The relevant CFIR constructs are presented in the Results. The Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies (FRAME-IS) is also utilized to provide a precise understanding of implementation adaptations.[36]

Methods

Overview

In this study, we designed and implemented a CDI checklist using strategies that were modified and adapted across hospital contexts. '*Intervention*' refers to the tool, a multicomponent CDI checklist in the form of a physical sticker with general diarrhoea management and CDI clinical interventions (Figure 1). The implementation strategies included development of stakeholder relationships, intervention champions, and training sessions, which together are called the '*implementation package'* in this study. As noted, we are assessing both the intervention tool and the implementation strategies by examining intervention uptake - the use of the checklist and its effect on measurable CDI care provided, and CFIR constructs associated with uptake. Across three hospitals the intervention did not change, but the implementation package was modified and adapted at each hospital. Modifications to the champions implementation strategy were further detailed using the FRAME-IS.

Ethics and Participating Hospitals

This study received approval from the University of the Western Cape (Ethics Reference Number: HS/16/1/24), the National Health Laboratory Service, Western Cape Department of Health, and the participating hospitals. The four hospitals included in the baseline epidemiology study were invited to participate. All invited hospitals were public district level hospitals in the Cape Town metropole. Three hospitals accepted the invitation, volunteering to participate in the study intervention and implementation, and one hospital declined to meet with the research team at the time of implementation.

Setting

South Africa has the greatest income inequality in the world, and the urban area surrounding Cape Town is still marked by a deep history of racial

segregation.[37] [38] The South African Department of Health, the national health system, serves 84% of the population. Meanwhile the private sector serves those who can afford it, approximately 16% of the population.[39] The cost to use the public health system is adjusted based on income, embodying a right to healthcare approach.[40] District level hospitals, also known as secondary level hospitals, often provide care for complex patients suffering from human immunodeficiency virus (HIV) and tuberculosis (TB), and patients of all ages, including the elderly with chronic conditions.[41] The hospitals included in this research averaged 265 inpatient beds and had similar but limited government funded resources (e.g. paper health records). The South African Department of Health's organizational structure is similar to many public sector national health systems globally. Overall, the health system experiences many of the same challenges as other LMICs in Africa and globally, such as staffing shortages and overcrowding.[42] Healthcare professionals, including pharmacists, are unevenly distributed to the private sector.[43–44] Clinical pharmacy services are in very early stages or non-existent at many in public sector hospitals, but have advanced substantially in South Africa, especially in the private sector.[44-46] The tangible resources needed for CDI treatment (e.g. gloves, gowns, antibiotics, soap) are usually available within the hospitals. However, they are not always utilized, potentially due to knowledge gaps and/or a lack of awareness of the infection.[17] [18]

The Western Cape Department of Health includes 237 clinics, 24 district hospitals, five regional hospitals, one tertiary children's hospital, and two tertiary adult hospitals. From expert and stakeholder feedback, we chose to base this research at the district level due to local need for understanding CDI and designing interventions.

Intervention and Implementation

The intervention was identified and developed in four phases that mirror quality improvement principles and are an adapted version of the Plan, Do, Study, Act cycle.[47] The phases are summarized with **Figure 2**. Details on the steps within each of these phases are presented in **Table 1**. The Expert Recommendations for Implementing Change (ERIC) strategies utilized are also named and further

detailed in **Table 2,** including details on the stakeholders, healthcare providers and administrators, and pharmacy students engaged with this reseach.[35] The research team selected the initial ERIC strategies utilized in Step 1 informed by quality improvement training early in the project development. The topic area and specific project was selected by internal South African leaders, Department of Health administrators and healthcare providers (Table 1). The intervention and implementation package were determined collaboratively by the research team with input and advice from local stakeholders. During pre-implementation stakeholder engagement meetings, the plan for implementation was discussed. During these meetings the implementation plan was adapted to meet the level of interest and availability of personnel at each hospital.

Ultimately, the 'Diarrhoea alert' CDI checklist, was developed and implemented with education sessions informed by the local context. The checklist is shown in **Figure 1** with its application to the medical record order form. No modifications were made to the intervention between the hospitals; the intervention invariably maintained two core elements: the checklist and items on the checklist.

Post-implementation quantitative medical records data were collected and post- implementation interviews were conducted to assess the implementation and intervention effects. CFIR is the conceptual framework used to analyze study findings, including a description of the implementation process and CFIR constructs associated with use of the intervention or uptake.[34] Implementation strategy adaptations, including modifications to how the intervention was implemented (i.e. the implementation package), were documented with the new FRAME-IS, which both mirrors and builds on the original FRAME that documents intervention modifications.[36 48 49] We applied all seven FRAME-IS modules, including the optional modules, to the champions implementation strategy, as it was the most substantial implementation package modification between the three hospitals.

Data Collection

Post-implementation a retrospective medical records chart review collected patient characteristics, CDI management, and outcomes (e.g., in-hospital

mortality). Patient test results were collected from the National Health Laboratory Services. Medical records for patients hospitalized with a *C. difficile* test order during the 90 days following a 2-week implementation and training period were reviewed. Outpatient test results were excluded. The research team summarized collected data on the steps of CDI care provided and patient outcomes, which was later presented to each participating hospital through formal presentations and individual meetings as interest and schedules allowed. The post-implementation data collection followed the methods of the published baseline epidemiology and CDI management study.[18] Briefly, the outcomes and care measures included: oral and/or intravenous rehydration, contact precautions, use/discontinuation of contraindicated loperamide in patients with CDI, antibiotic treatments, infection prevention and control precautions, and in-hospital mortality.

Post-implementation semi-structured qualitative interviews were conducted with individual health care providers at Hospitals 1 and 2: nurses (n=2), physicians including medical directors and administrators (n=7), pharmacists (n=2), nurse managers (n=2), and IPC nurses (n=1). Focus group discussions were also conducted with available nurses on hospital wards (n=6 focus groups, ~4-9 nurses/focus group). Audio files (N=20) from these interviews were transcribed verbatim, and two researchers coded the transcripts a priori to CDI workflow steps, feedback on the intervention, and the implementation process.

The research team was available for questions from the local implementation leads at Hospitals 2 and 3 before, during and after the 2-week implementation and training period. The research team maintained communication with the local implementation leads at Hospitals 2 and 3 to answer questions and collect information regarding their experience and the intervention status via in-person meetings, text messages, emails, and phone conversations. Note, implementation at Hospital 3 occurred after post-implementation interviews at Hospitals 1 and 2.

CFIR Analysis: Preparation of results and CFIR framework application

A CFIR analysis was conducted with the following steps. The research team pragmatically applied the CFIR framework to results from the qualitative

interviews, observations by research team members, and quantitative patient outcomes data in order to identify drivers and barriers to implementation and to understand differences in uptake at the three sites.[50]

The research team chose a qualitative approach to the CFIR analysis to produce translational results and a reproducible description of the intervention and implementation package, while continuing to strengthen collaborative partnerships with community stakeholders.[51] Producing robust numeric ratings was not a priority of this project and thus not performed. The relevance of the CFIR constructs was determined following a multi-step filtering and assignment process.

First, LL reviewed all 39 CFIR constructs, including the "Detailed Description" and "Codebook Guidelines" as available at the https://cfirguide.org/constructs/ website and then described in narrative and outline form the relevance of each applicable construct. Constructs that were non-applicable were excluded. Considering the data available and feasible scope of this study we chose to focus on three CFIR domains: 1) the Intervention, 2) the Inner Setting, and 3) the Implementation Process. The Outer Setting was not analyzed because all hospitals were affected by the same complex socio-cultural history, national politics, and Department of Health provincial- and national-level policies. The project was designed as a system-level intervention and was not intended for individual level analysis. Thus, the Individuals Involved domain was not analyzed. Finally, LL and RC discussed these methods and construct results.

In the second CFIR analysis step, constructs from the CFIR domains Intervention, Inner Setting, and Implementation Process were assigned to high or moderate relevance categories. Moderate constructs with overlapping findings were consolidated to the most pertinent construct. Constructs with low relevance were excluded. TE provided feedback on this construct list, relevance assignments, and drafted descriptions, emphasizing aspects of construct details. The 'Planning' construct was then excluded as the key aspects were described in other more substantiated constructs.

Third, adjustments in the relevance assignments were made. Specifically, during subsequent iterative drafts of the manuscript, the following construct changes were made:

- Intervention: Complexity was moved to highly relevant and Evidence Strength and Quality was moved to moderately relevant;
- Inner Setting: Leadership Engagement was added;
- Implementation Process: Reflection and Evaluation construct, originally unassigned, was designated as highly relevant to complete the description of the implementation.

In this way, constructs that were unique to this intervention and those that described the intervention's level of uptake between hospitals remained in the highly relevant category. No other changes were made to the relevance distinctions. For the sake of focus and brevity, moderately relevant CFIR constructs were presented in the results table with further details explained in the **Appendix**.

Ultimately, findings were reviewed by all co-authors, including local healthcare providers from the participating hospitals. The Standards for Reporting Qualitative Research (SRQR) were reviewed as a checklist for describing our qualitative research.[52] This study presents the relevant pre- and post-implementation feedback and post-implementation findings within the FRAME-IS and CFIR frameworks to frame the intervention development and explain the implementation process.

Results

Uptake or adoption of the checklist intervention was highest at Hospital 2, and low at Hospitals 1 and 3. Differences in adoption were apparent from the qualitive interview data, conversations with implementation leads, and the retrospective review of patient records with *C. difficile* test orders during the 90-day post-implementation phase. Detailed outcomes from Hospital 2 are in the Appendix: Reflecting and Evaluating.

Implementation Strategy Modifications and Adaptations with FRAME-IS

The implementation package consisted of the strategies detailed in **Table 2**, under the categories: Develop stakeholder interrelationships; Evaluative and iterative strategies; Train and Educate Stakeholders; and Support Clinicians. The implementation package was adapted at the three participating district level

hospitals. Training sessions were led by the implementation lead(s) and adapted to resources, available and interested personnel at each hospital.

Project implementation leads were appointed by the organization and research team for the project based on available resources and interest (external lead researcher at Hospital 1, registrar and student at Hospital 2, pharmacy intern at Hospital 3). The 'who, what, when, and why' of these modifications to the champions implementation strategy are named with the FRAME-IS (**Figure 3**). In this study the implementation leads served as champions; however, organizational support to empower the champions to lead, and their ability to drive through the intervention and overcome resistance varied between the hospitals.

Training at Hospitals 1 and 2 was performed by the external project lead. At Hospital 2, a medical registrar (medical resident) and medical student took roles of local peer champions. The adaptation to include a registrar proved to be the most effective and key differentiating factor.

For implementation at Hospital 3, the lead researcher trained a local champion to lead intervention implementation and provide the training sessions. The lead researcher and this local champion conducted the first education and intervention training at one of the hospital wards together. The local champion completed the intervention implementation at Hospital 3 as a project for a 1-year pharmacy internship through the Department of Health with guidance from the research team. However, gaining internal physician support was challenging. Additional details regarding the training sessions and adaptations are described in the Appendix, Supplemental detail on training adaptations and CFIR constructs.

CFIR Constructs Results

This study uses the CFIR framework's replicable language to describe the intervention and results as well as to understand instances of high uptake and acceptance juxtaposed with resistance at hospital and individual levels. Highly relevant and moderately relevant constructs for the Intervention, Inner Setting, and Implementation Process are presented in **Table 3** and summarized in **Table 4**. Moderately relevant constructs and additional details on select highly relevant constructs are provided in the **Appendix**.

As stated in the methods, the results present the CFIR constructs most relevant and differentiating to the intervention and implementation. Highly relevant constructs are detailed here.

I. Intervention/Innovation

Adaptability, Complexity and Source

The specific checklist implemented in this study was informed by existing CDI checklists and input from internal stakeholders, including local healthcare providers, hospital administrators, and local students.[53] The research team designed the intervention to fit the local healthcare setting and resources available, and address the gaps in CDI management described elsewhere.[17 18] An intervention sticker for TB was already in use and appeared to work well in the public hospitals. The CDI intervention was adapted to be applied to the medical chart orders page, or 'blue board,' of all patients with diarrhoea. While initially designed as the 'CDI Checklist,' the research team later changed the name to 'Diarrhoea Alert' to prompt a screening of all patients with diarrhoea. The checklist served as an alert and simple job aid for the elements of quality CDI care (**Figure 1**; see Intervention constructs in **Table 3** and further construct details in the **Appendix**). With CFIR, complexity is the construct that corresponds to this intervention's simplicity. Across sites, health care providers liked the checklist design and often reacted during trainings and interviews that it was really 'quite simple.' The CDI antibiotic treatment recommendations were based on the 2015 South African Standard Treatment Guidelines in place at the time of development.[54] The revised guidelines released in 2020, recommend metronidazole for mild-moderate CDI and vancomycin for severe CDI.[15]

The intervention source and development are detailed in the methods and appear with ERIC implementation strategies in **Table 2**. The implementation package consisted of the strategies detailed in **Table 2**, under the categories: Develop stakeholder interrelationships; Evaluative and iterative strategies; Train and Educate Stakeholders; and Support Clinicians.

The implementation package was adapted at three district level hospitals but invariably the intervention maintained two core elements: the checklist and items on the checklist. Training sessions were led by the implementation lead and adapted to resources, available and interested personnel at each hospital as previously described.

Hospital 4 was not yet ready for the intervention during the implementation phase at Hospitals 1-3. Requests to introduce the project and gain necessary approvals were unsuccessful. However, the research team was able to present the project to Hospital 4 with the intervention results and changes in quality of care observed at Hospital 2 one year later. Hospital 4 then added a 'Diarrhoea Alert' block checklist permanently printed on the bottom right corner of the inside page of the blue board for all patients. This adaptation reduced the size of the checklist and avoided disruption to the front nursing orders page.

II. Inner Setting

Leadership Engagement, Tension for Change, and Relative Priority

All hospital sites required engagement of the hospital Chief Executive Officer or another executive-level representative before implementing the project. However, Hospital 2 leadership, executive leaders and front-line consultants (attending physicians), more widely communicated their support, increasing the tension for change and CDI intervention's priority. For example, influential senior consultant physicians invited the intervention for presentation at the weekly department of medicine meeting including consultant and physician trainees. Pre-implementation, the research team gathered feedback for adaptation, and then post-implementation presented the results at these department meetings.

Overall, the epidemiology and outcome results proved current quality of care was an intolerable status quo, with mortality at 30% and treatment inconsistent with global guidelines or not provided at all.[18] At the time of implementation, these epidemiology results were not yet published. Understandably, healthcare providers perceived TB and HIV as higher priority infectious diseases; South Africa has the greatest number of people living with HIV in the world and TB is a leading cause of death in people with HIV.[55 56] Nevertheless, Hospital 2 recognized the potential

for the intervention to facilitate needed change and improve quality of care with evidence-based interventions. Key opinion leaders at Hospital 1 did not perceive the need for change; some providers did not see CDI as a problem.

III. Implementation Process

Engaging & Reflecting and Evaluating

Engaging: Stakeholders

Overall, the research team engaged stakeholders, opinion leaders, peers, and experts similarly across the included hospitals as described in the methods, **Table 1**, and the *Leadership Engagement* construct in the Inner Setting domain (**Table 3**). Healthcare providers who were to use the new checklist were also engaged in the project with interviews and focus group discussions before and after implementation as described in the methods. Front-line provider stakeholders were engaged with the CDI education and intervention training sessions. These sessions included a socially engaging component with the distribution of "CDI Trained" buttons/badges to staff who completed the sessions. The buttons served to remind staff of the intervention, engaging those who may have missed the training, and create a community around the implementation process. The number of providers who became strong project champions varied substantially between sites.

Engaging: Opinion Leaders and Champions

Support from opinion leaders for the intervention was a major distinguishing construct between hospitals. Some of these opinion leaders were also champions for the intervention. Initial contact with opinion leaders was made by the external project lead except when one of those opinion leaders introduced the project to their senior administrators (e.g. the head of a department contacting a hospital administrator).

Project implementation leads were appointed for the project based on available resources and interest (external lead at Hospital 1, registrar and student at Hospital 2, pharmacy intern at Hospital 3). At Hospital 2, one of the project leads was an opinion-leading registrar. The registrar was a respected peer physician role model and informal leader; his opinion was valued by both senior and junior staff

across the hospital. Together with the Department of Internal Medicine opinion leaders, the project leads were able to increase uptake at Hospital 2.

At Hospitals 1-3, nurse managers and administrators, including IPC and nurse educators, were engaged in the project. They accepted the project, recognized the need for the intervention, and affirmed its potential; however, they did not champion the project. Similarly, IPC nurses and nurse educators were engaged and supported the project but did not have as much influence as the consultant physicians. However, training sessions were introduced by the senior nurse administrators, nurse educators, and/or IPC nurses. These introductions were instrumental for building trust with the frontline staff. The training sessions were essential for creating awareness about CDI and its complications, as many of the nurses had limited awareness/knowledge preceding the sessions.[17] While nurses supported the intervention, they did not take ownership or see the intervention as part of their daily tasks. Nurses across the hospitals did not advocate for the intervention at the level the physicians championed at Hospital 2.

Furthermore, departments peripheral to internal medicine, such as surgery and emergency medicine, were also engaged and provided support for the intervention at both Hospital 1 and Hospital 2. Emergency medicine physicians were more supportive at Hospital 2 than Hospital 1. While Hospital 1 leaders were supportive, they did not have the same level of influence that consultants at Hospital 2's Department of Medicine had on other providers. The Hospital 2 consultants were then able to facilitate successful recruitment of staff, nurses, and junior physicians to participate in the intervention. As a result, the strong opinion leaders, including the senior level physicians, who championed the intervention at Hospital 2 were able to overcome indifference toward the intervention.

Reflecting and Evaluating

Preliminary assessment of progress and impact of the implementation pilot included the quantitative data from patients with CDI test results, observations, and qualitative interview data. Despite perceived challenges and low use at Hospital 1, the increase in CDI testing and awareness observed in post interviews indicates that there was an increase in CDI knowledge due to the implementation package. The centralization of printing checklists for Hospitals 1 and 2 suggests that the

implementation package initiated became a sustained change in organizational structure.

Comparison of our baseline data from four area hospitals (including Hospital 2) and Hospital 2 baseline results alone to post-implementation results signal improvements in CDI management and patient outcomes (**Appendix**: Reflecting and Evaluating). The results were not statistically significant nor was the study designed to detect statistically significant differences due to the short follow-up period. Measurable progress in improving quality of care and implementation uptake was greatest at Hospital 2.

Overall, the implementation of the intervention was associated with a self-reported heightened awareness and increased use of evidence-based CDI practices at the participating South African hospitals. Furthermore, the intervention demonstrates the capacity and potential of the "Diarrhoea Alert" to improve the quality of CDI care in South Africa when appropriate champions are engaged in the implementation effort.

Discussion

This study achieved its objective of developing a context specific intervention for CDI and identified key constructs for intervention uptake in South African public sector district level hospitals. This study identified key implementation science constructs that uniquely distinguish high intervention uptake at one hospital compared to two other South African district level hospitals with similar available resources and organizational structure. The new FRAME-IS is regarded as the first framework to be specific to implementation strategy modifications; we provide one of its first applications.[36] The FRAME-IS documented how the most relevant ERIC implementation strategy utilized, 'Identify and prepare champions,' was adapted to fit the interest and available personnel at each site with a co-creation approach. These changes in personnel leading the intervention were made proactively, prior to implementation, and related CFIR constructs emerged as highly relevant to the intervention's success.

First, tension for change was one of the most relevant constructs to distinguish uptake between the hospitals. The tension for change and prioritization communicated from leadership at Hospital 2 supported high intervention uptake. An academic partnership with the tertiary hospital, specifically the AMS ward rounds (Structural Characteristics), uniquely supported this tension for change at Hospital 2. Second, the individuals who championed the intervention at the hospital with a greater tension for change uniquely supported the intervention and contributed to its success. A position of influence and investment appeared to be a required characteristic of the champions to support intervention uptake. Additional CFIR constructs that proved to be highly relevant were intervention complexity and stakeholder engagement. The results imply strategies to engage low resource hospital settings without strong academic partnerships must adapt. The relevance of this work is that it unveils unique and universal challenges in South Africa that can be considered for how this applies to other low resource settings. Ultimately this study strives to promote the use of evidence-based practices for identifying, treating, and preventing CDI in low resource settings, and adds to the growing application of implementation science theories and frameworks in LMICs.

Implications from this research can be applied to pharmacy-led and interprofessional interventions in low-resource settings. A recurring theme in South Africa was the importance not only of champions' influence or seniority but also their level of investment in the project. For example, at Hospital 2, the senior registrar (i.e. resident) and medical intern who championed the project had strong investment and the support of seniority to influence uptake. In contrast, the pharmacy intern at Hospital 3 was highly invested in the project but lacked seniority to influence uptake and spread change. Culture within professions and hierarchy among groups contribute to the challenges of interprofessional teamwork; meanwhile interprofessional communication is essential for patient safety.[57 58] Broadly, South Africa can be categorized as having a moderate power distance where hierarchy is accepted and followed.[59] Healthcare providers lower in the social hierarchy may not speak up to issues they perceive, threatening patient safety.[58 60] The results of this study, specifically the key differences in uptake associated with the profession leading the intervention, is consistent with prior work

in South Africa that a healthcare hierarchy seems predominant and negatively affects interprofessional communication.[61] These cultural factors in South Africa may have also influenced the observed reluctance from nursing staff to take ownership of the intervention across the three hospitals. Thus, there is a crucial need to address inner setting factors such as readiness for change and psychological safety to support interprofessional interventions in the context of low resource settings.[28 62-65] Pharmacy-led interventions must also be mindful of forming interprofessional teams that are informed by the institutional culture and socio-political context.

Strong academic partnerships and a culture of supporting new initiatives also distinguish Hospital 2 from the hospitals with low uptake. Broadly, community academic partnerships are described in implementation science research as a critical component to implementing evidence-based practices and a cornerstone of many academic programs[66] To various extents, this project utilized recognized strategies, specifically: identifying barriers and facilitators to implementation, facilitating interactive problem solving, tailoring strategies, promoting adaptability, and auditing and providing feedback during the implementation phase. While the research team engaged healthcare stakeholders throughout this research, a community advisory board, a strategy not deployed, could strengthen this intervention, uptake, and systematic evaluation of these strategies.[66]

Finally, the straight-forward CDI intervention enabled its success at Hospital 2, and it could support sustained and scaled intervention. Simple interventions are more likely to be effective, and thus evermore crucial in overburdened public hospitals.[67, 68] The checklist can now be printed for the Western Cape hospitals on 'tender', a centralized procurement process all government facilities follow.[69] The checklist can operate without intervention from the research team, should healthcare personnel continue to use the checklist and the administration sets this expectation. The adaptation of the checklist being printing directly onto the prescription chart Hospital 4 is a sustainable and scalable iteration. Training, monitoring and providing feedback on the checklist's use could be provided through mechanisms for IPC monitoring already in place as well as be included in IPC training already routinely provided. Scalability is likely because the personnel,

physical structure, and resources available within district level hospitals are very similar across the Western Cape. However, micro- and socio-cultural differences exist within each hospital, such as those that emerged in this study. Across South Africa, variations may exist in provincial level priorities, administrative structure, and funding. The National Department of Health could scale intervention dissemination in the Western Cape and across South Africa. Adaptation is likely needed to fit province level differences in supplies, such as the prescription chart and order forms. Globally, the intervention may also be relevant to other governmental health systems. A fidelity assessment of both the sticker and the embedded prescription chart checklist form is needed to guide continued improvement.

Limitations

This study is a relatively small-scale study in a broadly understudied setting. Time to develop the implementation package, implement, and collect post-implementation results was also short. However, the research identified compelling themes between the hospitals. The results may be generalizable to healthcare settings outside of the Western Cape, South Africa with similar resources, challenges, and education systems. Researchers have adapted and applied the CFIR framework with and without numeric valence ratings assigned to constructs, both prospectively and retrospectively.[31 70 71] Earlier integration of the CFIR framework in this research could have strengthened the analysis and is recommended.[31 71] For example, our a-priori semi-structured interview guide was not structured to collect sufficient details for individual level analysis. This is an area for future research. Yet, we were able to detail facilitators and barriers to CDI care in a prior qualitative study, and apply the implementation science principles described in the methods.[17] A limitation of the analysis is that the CFIR dimensions are not quantified, but nevertheless they identify the constructs that are strongly associated with uptake through a process of author consensus. Additionally, such investigator bias, including those leading the project and key collaborators from South Africa and the United States cannot be extracted. To reduce this bias, qualitative interview data was coded by two additional researchers less directly invested in the study results.

Some authors were involved in all or select phases of the intervention development, implementation, data analysis, and reflective analysis. The CFIR conceptual framework also aided in structuring a systematic evaluation of the intervention and implementation. Accordingly, this participatory approach is both a strength of the research process and a limitation of the results.

Conclusions

This study provides a health systems strengthening intervention for CDI that is both needed and uncomplicated, in an understudied LMIC setting, and an analysis of the intervention uptake with the CFIR and FRAME-IS frameworks. This research provides a breakdown of the intervention development, implementation, and outcomes at three district level hospitals in Cape Town, South Africa. The results show uptake was highest in the hospital with tension for change, influential champions, and existing academic partnerships. The FRAME-IS precisely highlights how proactive collaborative implementation adaptations supported intervention uptake. In understudied settings with fewer academic connections, implementation researchers should first assess readiness for change and then test implementation strategies that could support collaborative intervention and implementation development.

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Table 1. Project phases with steps outlined from problem identification through results

PHASE I: Identify and analyze problem		
STEP 1	Stakeholder engagement and identification of CDI need in South Africa	The innovation area, Antimicrobial Stewardship (AMS), was selected by internal South African leaders, Department of Health administrators and healthcare providers. Subsequently a 'Strengths, Weaknesses, Opportunities, and Threats' or SWOT analysis of AMS projects was conducted, and CDI was selected as the specific project due to the scarcity of available data on CDI at the district level in the Western Cape province. A mixed methods research protocol was developed and approved.
STEP 2	Pre-intervention retrospective review of CDI patient care and outcomes	An CDI epidemiology and outcomes study was conducted to serve as baseline data for the intervention and provide data on the magnitude of CDI in public district hospitals in South Africa. Identified opportunities to improve patient care are also included in the published outcomes study.[a]
STEP 3	Stakeholder engagement on CDI	Pre-intervention qualitative interviews and observations mapped CDI workflow, including steps to identify, diagnose, treat, and prevent CDI, with identified barriers and facilitators to CDI care.[b] Interviews and focus groups gleaned information about what resources already existed and what elements of a CDI intervention would be both possible and helpful.
PHASE II: Develop intervention and implementation package		

STEP 4	Consideration of local context and synthesis of data to develop the intervention and implementation package	Local context gathered through **Phase I** of the project informed the intervention and implementation package. Elements of interventions already successful in the participating hospitals and feedback from both local stakeholders and infectious diseases leaders were considered. A literature review of existing checklists and bundle interventions globally for CDI was performed. The synthesis of these results led to the development of the intervention, the 'Diarrhoea Alert,' or CDI checklist, and implementation package, including tailored education sessions.
PHASE III: Implement		
STEP 5	Put into practice the intervention and adapt implementation package	We continued to adapt the implementation package for the intervention created in Step 4 to meet the local environment at each hospital based on feedback from local healthcare providers. Implementation at Hospitals 1 and 2 began with a trial of the training session at Hospital 1 delivered by the lead researcher, continued with adapted training across hospital wards and departments, and concluded with local champions, or individuals who dedicated themselves to the intervention and conducted follow-up. A more independent implementation model was utilized at Hospital 3 in order to see the effect of a train-the-trainer model for the project. The lead researcher trained a local champion to lead intervention implementation. Finally, implementation at Hospital 4 did not occur until after results from

		Hospital 2 were presented to Hospital 4 leadership.
PHASE IV: Collect and examine results		
STEP 6	Post-implementation engagement and interviews	Post-implementation interviews and focus groups were conducted to gather qualitative data about the efficacy of the intervention (i.e. how was the checklist being used or not, how were patients with diarrhoea and CDI being managed, what did the providers know about CDI post implementation) and feedback for future adaptations. Participants were recruited with purposive sampling of both providers who were previously engaged with intervention implementation and providers unfamiliar to the research team. An informed consent document, approved by the ethics committee, was provided to participants, participants provided written consent, and participants could decline participation at any time.
STEP 7	Preparation of qualitative data	Twenty interview audio files were transcribed verbatim, and two researchers coded the transcripts a priori to CDI workflow steps, feedback on the intervention, as well as the implementation package. The qualitative data

		analysis software NVIVO (Version 11, QSR International) was used for coding. Discrepancies in coding were discussed and resolved.
STEP 8	Preparation of results, CFIR[c] framework application, and FRAME-IS[d] application	The focus of this analysis: the CDI intervention development, implementation process and adaptations were analyzed to understand differences in acceptance, uptake, successes, and failures of the CDI intervention.

a. Legenza et al. *BMJ Global Health* 2018

b. Legenza et al. *Antimicrobial Resistance and Infection Control* 2018

c. Damschroder et al. *Implementation Science* 2009

d. Miller et al. *Implementation Science* 2021.

Table 2. ERIC[a] implementation strategies used to develop the intervention and implementation

Strategy	Actions taken
Develop stakeholder interrelationships	
Conduct local consensus discussions & needs assessments (Table 1, STEP 1)	Conducted a country-wide qualitative needs assessment of the South African health system via 1.) scoping review of policies and published literature to identify national priorities, and 2.) discussions with stakeholders and providers at policy, administrative, supervisory, operational, managerial, and patient care levels. Antimicrobial Stewardship was chosen as the innovation area by those who conducted the needs assessment. Consulted with academic leaders at various universities across South Africa and in Cape Town. Narrowed needs assessment to the Western Cape province level. Consulted with stakeholders at policy level regarding needs in both public and private sectors (e.g. Pharmacy Services, Western Cape Department of Health). Consulted with both infectious disease leaders in public and private sectors (e.g. South African Department of Health, private sector heads of microbiology). Consulted with internationally recognized infectious disease researchers and clinicians in South Africa and the United States, including those leading work in Antimicrobial Stewardship and *Clostridioides difficile* infection (CDI). Presented chosen problem (CDI) to leaders previously engaged in needs assessment and departments of internal medicine to affirm chosen problem was important and determine if clinical innovation to address it was appropriate.

Build a coalition (STEPS 1, 3, 4)	High-level hospital chief executive officers and administrators were engaged for project approval with the intervention. Heads of departments and managers assisted with introductions to the "educationally influential" and local opinion leaders to recruit and cultivate relationships with partners in implementation effort.
Conduct educational meetings & Inform local opinion leaders (STEPS 3,4)	Conducted pre-intervention interviews and meetings with "educationally influential" hospital administrators, senior physicians, infection prevention and control nurses, nurse educators, and pharmacy managers to teach them about the intervention as well as local opinion leaders with hope that they would influence colleagues to adopt the intervention.
Identify and prepare champions (STEP 5)	Identified and prepared champions at each hospital who would "dedicate themselves to supporting, marketing, and driving through an implementation, overcoming indifference or resistance that the intervention may provoke in an organization."[a]
Develop academic partnerships (STEPS 2-7)	Strengthened existing academic partnership between the participating Schools of Pharmacy. Engaged pharmacy students from both universities for shared training and skill-building with the research project, including partnership with the 1-year longitudinal research program for final year South African pharmacy students (two groups of students over two years) and inclusion of independent study and Advanced Pharmacy Practice Experience (APPE) students.
Use evaluative and iterative strategies	
Conduct local needs assessment	Conducted baseline CDI management and patient outcomes retrospective review including in-hospital mortality and identification of gaps in treatment and infection control.[b]

(STEPS 1,2)	
Assess for readiness and identify barriers and facilitators (STEP 3)	Identified barriers and facilitators through qualitative interviews with healthcare providers and stakeholders.[c]
Audit and provide feedback (STEP 5)	Visited hospital wards during implementation to audit use of the innovation and provide feedback to clinicians.
Train and Educate Stakeholders	
Develop educational materials (STEPS 4,5)	Developed training handouts and reference/reminder. Developed educational reminder/recognition wearable buttons.
Distribute educational materials (STEP 5)	Delivered educational materials in person during training and education sessions.

Make training dynamic (STEPS 4,5)	Tailored training to each healthcare profession (nurses, pharmacists, physicians). Included dynamic interactive learning delivery with open-ended questions and patient examples in training. Included examples to show when to apply the intervention that encouraged participant engagement in each stage of infection identification, diagnosis, treatment, and prevention. Provided in-person reinforcement follow-up training in the ward and asked about current patient needs (patients with diarrhoea). Provided training individually to any providers who missed initial group training sessions.
Support Clinicians	
Remind clinicians (STEP 5)	Developed reminder posters for the intervention that were posted in the wards to prompt clinicians to use the intervention for applicable patients.

a. Powell et al. *Implementation Science* 2015

b. Legenza et al. *BMJ Global Health* 2018

c. Legenza et al. *Antimicrobial Resistance and Infection Control* 2018

Table 3. Intervention, Inner Setting, and Implementation Process highly relevant and moderately relevant CFIR constructs.

CFIR Domain		
Intervention		
Relevance	Construct	Theme
High	Adaptability	We adapted existing evidence-based CDI interventions and checklists to fit the local healthcare setting and resources available.
High	Complexity	The simple intervention avoided altering standard work processes, and instead simply triggered reminders to identify patients with diarrhoea, provide quality of care measures, test patients at risk for CDI, treat patients with CDI, and apply IPC procedures. Physically applying the checklist sticker to the blue boards of patients with diarrhoea was the most complex step.
High	Source	Internal South African leaders and local healthcare providers selected the innovation area via a participatory process.
Moderate	Evidence Strength and Quality	Awareness and perceptions of evidence-based CDI interventions and other bundle approaches varied among healthcare providers.
Inner Setting		
High*	Leadership Engagement	All three sites required engagement of the hospital Chief Executive Officer or

		another executive-level representative before implementing the project. Hospital 2 leadership showed the strongest commitment. The Hospital 1 executive leadership welcomed the intervention and appreciated its value but expressed some skepticism on the long-term sustainability. At Hospital 3, attempts to meet with consultant level physicians were sometimes unsuccessful; meeting requests were declined, ignored, and/or canceled at the scheduled time of meeting.
High*	Tension for Change	Hospital 2 leaders uniquely recognized the need to improve CDI identification and treatment.
High	Relative Priority	Providers prioritized TB and HIV above CDI. Concurrent IPC programs, such as hand hygiene trainings, lacked organization wide support.
Moderate*	Structural Characteristics	The social structure of the district hospitals included is similar to other public district level hospitals across Africa and other low resource healthcare settings. Uniquely, a weekly Antimicrobial Stewardship (AMS) ward round occurs at Hospital 2 and includes pharmacy and medicine presence along with trainees. The AMS ward round is often led by an infectious diseases expert from the tertiary teaching hospital/university.

Moderate*	Networks and Communication	The Department of Internal Medicine at Hospital 2 uniquely had a WhatsApp communication system for laboratory results, patient needs, and program reminders, including reminders about the CDI intervention.
Moderate*	Available Resources	Time and the personnel involved with the project were resources that varied for the implementation at each hospital. Tangible resources available, such as medications, IPC supplies (gloves, gowns, soap, etc.), and other supplies were similar at all publicly funded district hospitals.
Moderate	Access to Knowledge and Information	The barriers and facilitators study identified limited CDI knowledge as a major barrier to CDI treatment. The implementation process included CDI education and training materials in a digestible format. These materials, handouts, reminder posters, and the in-person training sessions on the ward or other convenient locations were similar across sites.
Implementation Process		
High	Engaging: *Stakeholders*	The stakeholder engagement process was most similar between Hospitals 1 and 2. At Hospital 3, the external researcher started stakeholder engagements (interviews) and trained a

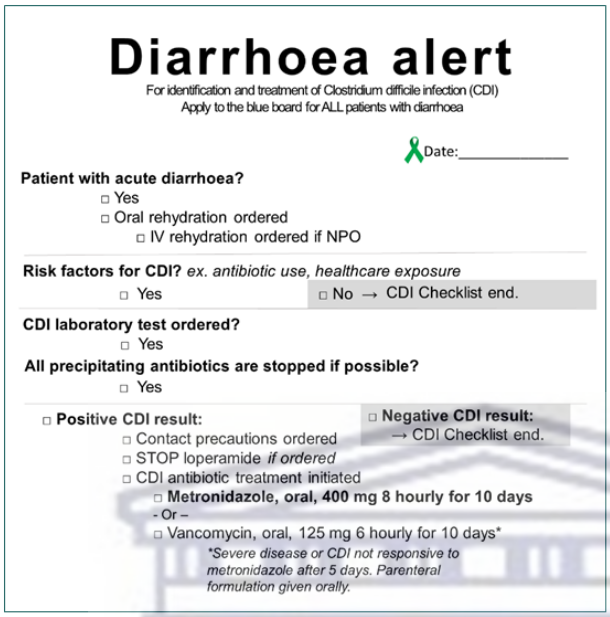
		pharmacy intern to continue engagements (training).
High*	Engaging: *Opinion Leaders and Champions*	Opinion leading Hospital 2 physicians uniquely influenced the intervention uptake.
High	Reflecting and Evaluating	An increase in CDI testing and awareness observed in post interviews indicates that there was an increase in CDI knowledge due to the implementation package. The lead researcher presented results at Hospitals 1 and 2 in person via formal individual and group discussions and presentations. Results at Hospital 3 were presented to the Western Cape Department of Health as part of the internship program. Results from Hospital 2 were also presented to the Department of Health and Hospital 4 during an invited presentation to hospital leadership.

*Uniquely distinguishes the hospital with high intervention uptake (Hospital 2) and differences between the three hospitals.

Table 4. Identified CFIR constructs with moderate or high relevancy to implementation

Relevancy	CFIR Domain		
	Intervention	Inner Setting	Implementation Process
Highly Relevant	• **Adaptability** • **Complexity** • **Source**	• **Leadership Engagement** • **Tension for Change** • **Relative Priority**	• **Engaging: Stakeholders** • **Engaging: Opinion Leaders and Champions** • **Reflecting and Evaluating**
Moderately Relevant	• Evidence Strength and Quality	• Structural Characteristics • Networks and Communication • Available Resources • Access to Knowledge and Information	

Figure 1. CDI intervention checklist* and CDI checklist applied to medical record order form



Diarrhoea alert

For identification and treatment of Clostridium difficile infection (CDI)
Apply to the blue board for ALL patients with diarrhoea

Date:_____

Patient with acute diarrhoea?
- ☐ Yes
- ☐ Oral rehydration ordered
- ☐ IV rehydration ordered if NPO

Risk factors for CDI? *ex. antibiotic use, healthcare exposure*
- ☐ Yes
- ☐ No → CDI Checklist end.

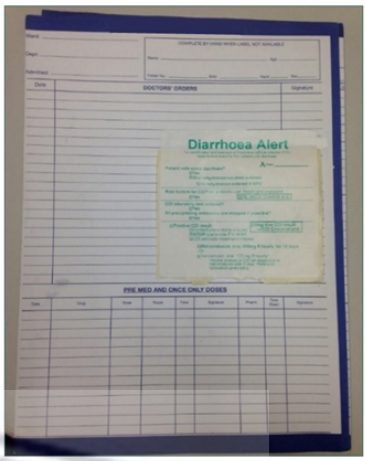
CDI laboratory test ordered?
- ☐ Yes

All precipitating antibiotics are stopped if possible?
- ☐ Yes

☐ **Positive CDI result:**
- ☐ Contact precautions ordered
- ☐ STOP loperamide *if ordered*
- ☐ CDI antibiotic treatment initiated
  - ☐ **Metronidazole, oral, 400 mg 8 hourly for 10 days**
  - - Or –
  - ☐ Vancomycin, oral, 125 mg 6 hourly for 10 days*

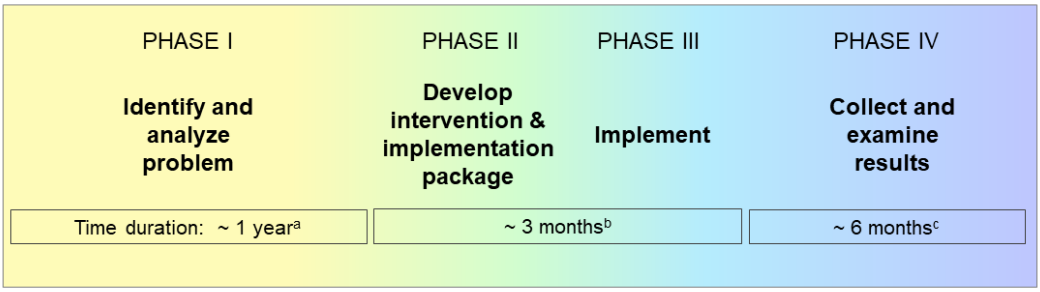
Severe disease or CDI not responsive to metronidazole after 5 days. Parenteral formulation given orally.

☐ **Negative CDI result:**
→ CDI Checklist end.



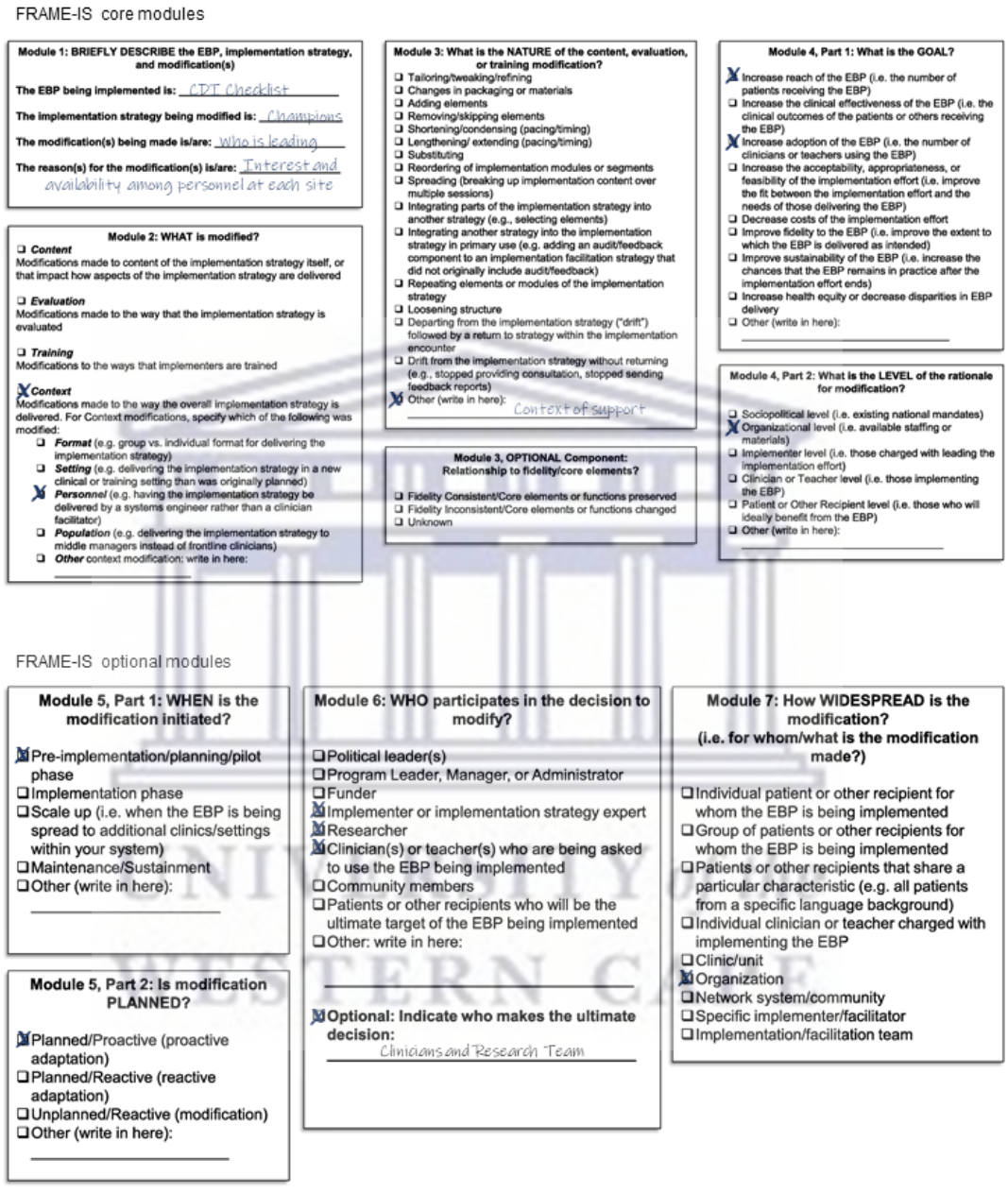
*Treatment follows the 2015 South African Standard Treatment Guidelines in place at the time the checklist was developed. The 2019 guidelines now specify metronidazole for treatment of mild to moderate *Clostridioides difficile* infection (CDI) and vancomycin for severe infection.

Figure 2. Study design in four project phases



a. Estimated total time includes time to develop protocol and obtain research ethics approval.
b. Estimated total time on site at hospitals preparing and implementing intervention.
c. Estimated total time collecting and analysing 90-day post-implementation results; does not include preparation of publication.

Figure 3. Adaptations to the champions implementation strategy contextualized within the Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies (FRAME-IS)[a]



a. Applied FRAME-IS adapted from Miller et al. *Implementation Science* 2021

Appendix: Supplemental detail on training adaptations and CFIR constructs

6.5 Contributions to the thesis

To the thesis this study fulfills **Objective 3** to: contextualize the CDI intervention and study findings with a conceptual framework.

In this chapter we detail our development of a CDI intervention informed by preliminary data and stakeholder feedback (Objective 3a), and analyse the CDI intervention development, implementation process and adaptations with the Expert Recommendations for Implementing Change (ERIC) strategies, CFIR, and FRAME-IS frameworks (Objective 3b). As described earlier, the manuscript of these results is accepted for publication in RSAP.

6.6 Novel contributions to knowledge and implications

The results provide a health-systems strengthening intervention for CDI that is both urgently needed and uncomplicated in the context of the understudied public-sector hospitals in Cape Town. The intervention uptake is analysed with the highly cited CFIR framework, and the implementation adaptions are detailed with the novel FRAME-IS, as one of its first applications. The results underscore how tension for change, influential champions, existing academic partnerships, and proactive adaptations supported the intervention uptake. The results also identify how testing of collaborative implementation strategies is needed in settings with fewer academic connections. The knowledge gained from looking at the successes and failures of intervention uptake can inform future implementations in this setting for CDI interventions and potentially other disease states.

7 DISCUSSION AND CONCLUSION

7.1 Novel contributions and interpretations

This thesis contributed to the fields of pharmacy, health systems strengthening, infectious diseases and IS. The results contributed clinically and statistically significant novel CDI findings, and the CDI intervention informed by this context. Each of the three results chapters had their own distinct approach to addressing CDI care. The first paper (Chapter 4) contributed previously unknown baseline data on CDI epidemiology and outcomes. The second paper (Chapter 5) explained how and why the gaps in identifying and treating CDI might be occurring with vivid qualitative data. Accumulating the qualitative and quantitative results created momentum for a context-informed intervention. The third results manuscript (Chapter 6) responded to the needs and opportunities identified with the CDI intervention and implementation package developed with local collaborators. The methods section of this final manuscript organised each phase of the project with named ERIC implementation strategies, including quantitative and qualitative methods from the starting point of identifying the topic area with local consensus discussions to reporting the intervention results to the participating hospitals. Finally, the third manuscript analysed the intervention and implementation with the CFIR and FRAME-IS frameworks, explaining differences in uptake among three public hospitals with theory-based constructs. Four notable contributions and interpretations are described below.

First, this thesis provided baseline data on CDI epidemiology, treatment and outcomes that could be used to design and measure quality improvement interventions (Objective 1). This study provided novel contributions in the determination of CDI patient characteristics and their association with mortality. The results identified TB as a new CDI risk factor. This thesis described the mortality of patients with *C. difficile* for the first time in district level public hospitals in sub-Saharan Africa: 29% of patients with a positive result died within 30 d compared to 8% of similar patients testing negative ($p < 0.0001$).[208] The

significant and independent risk of in-hospital mortality was 4.7 times greater than similar patients with *C. difficile* negative test results (OR 4.7, 95% CI 2.0 to 11.2; $p < 0.001$). While most patients treated for CDI received metronidazole, a gap of 29% of patients with a *C. difficile* positive result did not appear to receive any treatment and few patients received vancomycin (two patients [1.8%] as initial therapy and 16 patients [14.3%] as a change of therapy or additional therapy). As described in the literature review, the STGs at the time contrasted with evidence that vancomycin improved outcomes. The published abstract of early study results along with recommendations were provided to the STG Adult Hospital Level Expert Review Committee to support the guideline change to use of vancomycin as a first line agent for CDI patients with immunodeficiency. This national guideline change is expected to improve outcomes for patients with immunodeficiency and CDI in SA.

Second, detailed facilitators and barriers to CDI care were provided (Objective 2). The study underscored CDI knowledge gaps among providers, and how existing infection prevention and control supplies and practices could be applied to CDI patients to improve care.[187] Together, the findings from the epidemiology and outcomes study and the qualitative study filled gaps in determining the risks for CDI development and associated patient outcomes in low resource settings, as well as how CDI was managed and perceived in SA (Objectives 1 and 2).

Third, the results were incorporated to provide a contextualised CDI intervention (Objective 3). Finally, the intervention development and implementation analysis identified factors associated with differences in uptake across three hospitals. Our application of the adaptation framework, FRAME-IS, added new insights on how the adaptations to the implementation strategies were made proactively and collaboratively at the hospitals.[209] Often, adaptions are made in implementation as a reaction to unexpected adverse events, such as cancelled in-person meetings due to budget constraints.[48] Unique to the IS literature, our proactive adaptions to the champions strategy resulted in a positive change on intervention uptake at the high-uptake hospital.

7.2 Limitations

7.2.1 Epidemiology and outcomes study limitations

One of the limitations of the epidemiology and outcomes study was our retrospective approach and our inability to determine recurrent disease due to inconsistent records before and after the admission reviewed. Complete records were not available for all patients, and it was unknown whether the patient had prior or subsequent admissions that might have included symptoms and/or identification of CDI. As described in the publication,[208] an information bias might be present from a lack of knowledge of potential additional risk factors, prior hospitalisations and disease states. This limitation could be addressed only with improvements in the healthcare system's record management or a prospective approach to follow patients prospectively and follow initial cases of CDI for recurrence. However, this methodology would require more resources for patient follow-up and research administration.

The results of the research were generalisable to additional low resource settings with high prevalence of HIV and TB. The results were limited to the public sector and did not capture the extent of CDI risk factors and outcomes in the SA private sector where HIV and TB were less prevalent, but less restrictive antibiotic formularies might contribute to CDI risk. The private sector provided care to a minority of the population and was outside this study's scope focusing on the understudied low resource public sector.

7.2.2 Perceptions and practices study limitations

Results from the qualitative CDI perceptions and practices study were limited to the public sector hospitals included and might be transferable to similar settings. However, the results could not be generalised to a larger population due to the qualitative nature of the research. This limitation was unavoidable. As described in the results chapter, the findings were limited by our bias. Our approach of using

multiple qualitative coders might have reduced the research's bias. While our CDI knowledge scoring system was not validated, the results provided novel insights on provider awareness of CDI.

7.2.3 Intervention and implementation study limitations

We developed a modest checklist intervention in a relatively short time. However, the invention's simplicity was one of its major strengths. Results from the intervention development and implementation analysis were limited by the retrospective nature of the framework applications, as described in Chapter 6. Nevertheless, the intervention responded to the local AMS needs identified early in the design of this research. Then, the intervention addresses the concerning gaps in CDI quality of care and the high mortality associated with CDI identified in the first results chapter.

7.2.4 Summative limitations

Across this thesis, there was a bias toward improving the quality of care in SA. Our systematic approach of first documenting the quantitative baseline data and qualitatively coding pre-and-post intervention interviews with two coders addressed this bias. The IS frameworks applied to the entire intervention development process and resulting intervention uptake provided a structure to understand the strengths and weaknesses of this research and CDI intervention. Despite the limitations, the results provided novel and needed contributions. The baseline quantitative and qualitative data results could direct resources and support intervention implementation to improve CDI quality of care, including subsequent iterations of the CDI checklist. The CDI checklist tailored to low resource settings was one additional contribution.

7.3 Implications and recommendations

7.3.1 Implications and recommendations from thesis results

Chapter 4's results show that risk factors for CDI and current standards of CDI care in low resource settings were different than high resource settings. Improved CDI treatment and management was urgently needed due to the high mortality observed. As an implication of this study, TB should now be considered a risk factor for CDI in populations with high HIV and TB co-morbidity. This study shows that a positive CDI result increased the risk of in-hospital mortality.

Prior to the publication of this thesis's epidemiology study few studies examined the relationship of CDI and TB. One of these studies was the work by Pulvirenti et al.[77], who found a relationship between CDAD and TB medication and attributed the non-significant results to either TB itself or a more ill group of patients with more intensive antibiotic exposure. Our results found a significant association with TB comorbidity and CDI. The results from this thesis (Chapter 4) implied the association might be related directly to TB pathogenesis or TB medications, as opposed to generic antibiotic exposures or healthcare exposures.

Since the publication of our novel findings on the risk of CDI with TB, a study of CDI in a TB hospital in SA was published and found a vast majority of the strains (95%) were ribotype 017 (RT017) and all strains were multi-drug resistant. It was possible that RT017 was responsible for the severe disease and poor outcomes observed in this thesis. The study did not state the prevalence of HIV in the study population but stated many of the patients included were HIV positive. The authors concluded TB patients might be at increased risk for CDI.[204] Thus, the multi-drug resistant findings from the TB hospital study coupled with the high mortality observed in this thesis warranted heightened suspicion of CDI in the TB and HIV population.

The results on CDI perceptions and practices (Chapter 5) implied healthcare provider knowledge of CDI could not be presumed. Also, the results showed the risk of CDI mortality in patients with HIV and TB was not a top priority for the healthcare providers included here, indicating a low tension for change (i.e., the providers did not perceive the current situation as intolerable). Thus, interventions for healthcare provider efforts should include an introduction to the infection and its sequelae.

Mapping the provider interview responses to a workflow chart with the facilitators and barriers analysis (Chapter 5) revealed gaps in the system to ensure each step of CDI management was enacted. The inspiring part of the results was the availability of resources, procedures and mechanisms to manage CDI, and indications of some support for change and AMS. The qualitative thesis results implied that these measures could potentially be achieved with a low-cost intervention, such as the checklist developed as part of this thesis or a similar intervention.

While uncertainty remained around the cause of a higher risk of acquisition of CDI in patients with TB, the results of this thesis agreed with limited prior studies recommending that CDI must be a part differential diagnosis for patients with diarrhoea, especially those from populations with high HIV and TB prevalence. Providers in SA must have a heightened level of suspicion of CDI above current practices in this population because of the high risk of mortality. However, the results proved an urgent disconnect existed between the severity of CDI in the immunocompromised patients and the reality of care in SA revealed by this thesis. First, there was a lack of urgency perceived by healthcare providers per the qualitative study, and lower intervention uptake at two of the hospitals. Second, gaps in care and delays in CDI management measures existed in low resource settings per the quantitative study. Therefore, CDI interventions should address the consequences of CDI and steps of CDI identification, treatment and prevention to improve outcomes.

This thesis described a process for developing a simple evidence-based intervention informed by the local context, specifically the needs, gaps and available resources in low resource public district level hospitals. Our methods for developing the intervention and findings (Chapter 6) added to the field of IS by providing a practical application of the widely applied CFIR framework and the new FRAME-IS frameworks. These frameworks were applied to a common infection in an understudied and low resource setting. This research contributed to the literature unique and universal implementation challenges in SA that could be considered for scaling this CDI intervention and developing new interventions in similar low resource settings.

Finally, the study findings had implications that could be applied globally across settings. The results across the three studies underscored the complexity of CDI care and opportunities for pharmacy. Pharmacists could contribute recommendations for optimised antimicrobial treatment to prevent CDI and optimise CDI treatment. They could take an active role in providing CDI education to healthcare providers on preventing, identifying and treating CDI. This thesis provided an example for how pharmacy could collaborate with interprofessional teams to provide AMS and disease-state specific interventions. For examples on pharmacist interventions in epidemics including CDI, consider reviewing a continuing education article of epidemics authored by the candidate and published in the *Journal of The Pharmacy Society of Wisconsin* (Appendix O).[66]

7.3.2 Recommendations for future research

While this thesis found an association of TB and CDI, details of this relationship as a pathogenic attribution from the disease or from the associated antibiotic treatment were beyond this study's scope. Future studies need to delineate this distinction to better understand, treat and prevent CDI. Nevertheless, the baseline quantitative and qualitative data results could direct resources by providing evidence to support intervention implementation, including subsequent iterations of the CDI checklist. The simple CDI checklist intervention presented in this thesis addressed the

identified needs and considered the available resources. The intervention was well-received, yet uptake was inconsistent among the three hospitals. The CDI checklist and implementation package showed improvement in CDI care at the high-uptake hospital. Our CFIR analysis of this uptake (Chapter 6) detailed CFIR constructs and implementation adaptations that primed the high-uptake hospital for success, and these results could inform scaled CDI intervention implementations. Briefly, uptake of the checklist was low at the hospitals with lower tension for change and fewer academic partnerships. Successful implementation required strong peer champion support for uptake. Similar hospitals in low resource settings should look for these indicators of readiness to implement the CDI checklist intervention. Therefore, it is recommended that further implementation research take place in settings like the low-uptake hospitals to evaluate readiness for implementation and test alternative implementation strategies. Furthermore, while feedback from healthcare providers indicated the checklist was simple and easy to use, this study did not formally evaluate usability, feasibility, and acceptability. Note that the new CFIR Outcomes Addendum published in 2022 includes adoption as an implementation outcome.[180] These new outcomes could be evaluated in future implementations of the intervention.

7.4 Conclusion

This thesis fills multiple gaps in CDI literature with novel findings on CDI epidemiology and risk factors, perceptions, facilitators and barriers to managing CDI in limited resource settings. To our knowledge, this was the first time a significant association between TB and CDI was found. Results showed improvement in CDI quality of care and CDI patient outcomes was needed as patients were at high risk of CDI-associated mortality. CDI associated in-hospital mortality was 29% in the public district hospitals and might be similar in low resource settings in sub-Saharan Africa. The context-informed CDI bundle intervention provided by this thesis might lead to improvements in quality of care in SA hospitals and other LMICs. The context revealed in this thesis could inform refinement of future CDI interventions, along with wider implementation and

adaptations. Uptake of the CDI bundle intervention in SA public district hospitals was greatest at the hospital with tension for change, influential champions and existing academic partnerships. Further implementation research is needed to evaluate implementation strategies in settings with fewer academic connections and test proactive adaptations. Pharmacy-led interventions should form interprofessional teams that are informed by the institutional culture and local context.

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Appendix A: ***Journal of the American Pharmacists Association*** **CDI vaccine publication**

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VACCINE UPDATE

Vaccines in development for the primary prevention of *Clostridium difficile* infection

Laurel M. Legenza, Susanne G. Barnett, Warren E. Rose

The Centers for Disease Control and Prevention (CDC) lists *Clostridium difficile* infection (CDI) as an urgent threat because of its increasing incidence, high-cost complications, readmission rate, and mortality. Clinical manifestations of CDI range from mild to severe diarrhea and systemic, life-threatening complications such as pseudomembranous colitis, toxic megacolon, and sepsis. CDC estimates that 453,000 cases occur each year in the United States and 15,000 deaths are attributed directly to CDI.[1] The annual economic burden from healthcare costs in acute-care facilities associated with CDI in the United States is approximately $4.8 billion.[2] Following initial treatment, CDI recurrence is approximately 25% and increases to 45%-65% after a first recurrence.[3]

Antibiotic use is a primary risk factor for CDI, with exposure to broad-spectrum antibiotics and long treatment durations further increasing the risk of infection.[4,5] Antibiotic exposure can disrupt the normal colonic microbiota and allow for *C. difficile* proliferation and superinfection. *C. difficile* produces 2 enterotoxins: toxin A and toxin B. Toxin B is essential for disease virulence.[6] Additional risks for developing symptomatic CDI include recent hospitalizations, proton-pump inhibitor use, age greater than 65 years, chemotherapy use, inflammatory bowel disease, and immunocompromising conditions.[6,7] The ability to mount an immunoglobulin G response against *C. difficile* toxin may reduce risk of developing CDI or lower the severity of disease.[8] Novel strategies for primary prevention—that is, preventing the infection before it occurs—are especially vital in at-risk populations.

The Infectious Diseases Society of America recommends several infection control and prevention strategies for CDI.[9] Contact precautions for patients with CDI (e.g., gown, gloves, hand hygiene) are advised until diarrhea resolves. When available, isolation rooms must be used when patients with CDI are hospitalized and then thoroughly decontaminated after their stay.[9,10] In addition, antimicrobial stewardship programs, which focus on increasing the appropriateness of antibiotic use, decrease CDI incidence and are an integral part of infection prevention measures.[11]

Despite infection prevention and control efforts, CDI rates continue to increase annually.[12] This increase is in contrast to the decreasing rates of other serious health care–associated infections.[12,13] *C. difficile* is now the leading cause of health care–associated infections.[14,15]

Novel therapeutic and host preventative strategies are needed to combat this growing problem. Numerous therapeutic strategies have been formulated in recent years with the aim of treating CDI and reducing recurrence rates, such as the oral antibiotic fidaxomicin (approved in 2011) and the intravenous monoclonal antibody bezlotoxumab against *C. difficile* toxin B (approved in 2016). Fecal microbial transplantation and administration of nontoxigenic *C. difficile* spores are optional biologic strategies, but they might not prevent CDI with future antibiotic use.[16] In an effort to provide primary prevention of CDI, several vaccine candidates are now in development. These vaccines contain components of the *C. difficile* toxins to lead to a serum antibody response or seroconversion (Table 1). If approved, CDI vaccines could address the need for long-term primary CDI prevention.

Phase III vaccine: Cdiffense

Cdiffense, developed by Sanofi (NCT01887912), is the CDI vaccine in the latest stage of development. It is a formalin-inactivated toxin A and toxin B product to prevent primary symptomatic CDI. The intramuscular toxoid injection is currently in randomized phase III studies, with the primary outcome of symptomatic and microbiologic-confirmed CDI cases during a period of up to 3 years post-vaccination. Secondary outcomes will measure serum antibody concentrations and injection-site reactions. Inclusion criteria require age greater than 50 years and recent hospitalization with systemic antibiotic use during 12 months before enrollment or planned hospitalization for surgery.

Send your immunization questions to the *JAPhA* Contributing Editors who coordinate the **Vaccine Update** column:

■ Mary S. Hayney, PharmD, MPH, BCPS, Professor of Pharmacy, School of Pharmacy, University of Wisconsin, Madison (mary.hayney@wisc.edu).

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Table 1
Clostridium difficile infection vaccine products in development

Vaccine product	Sponsor	Phase	Vaccine formulation	Population studied	Age (y)
Cdiffense	Sanofi	Phase III	Formalin-inactivated *C. difficile* toxin A and toxin B	Adults with CDI risk factors[a] and no self-reported CDI history	>50
VLA84	Valneva	Phase II	Recombinant fusion protein of *C. difficile* toxin A and B binding regions	Healthy adults without prior or suspected episode of CDI	≥50[b]
3-dose CDI vaccine	Pfizer	Phase III	Genetically modified and chemically treated recombinant full length *C. difficile* toxin A and toxin B	Adults with CDI risk factors[c] and no prior CDI history	50-85

Abbreviations used: CDI, *Clostridium difficile* infection.
[a] Inclusion criteria require age greater than 50 years and recent hospitalization with antibiotic use in previous 12 months or planned hospitalization for surgery.
[b] Results stratified: 50-64 and ≥65 years old.
[c] Inclusion criteria require age greater than 50 years and systemic exposure to antibiotics in the previous 12 weeks or an increased risk of future health care exposure.

Patients with previous CDI, active diarrhea, history of inflammatory bowel disease, or immunodeficiency are excluded. A schedule of injections on days 0, 7, and 30 with 100 mcg antigen with aluminum hydroxide adjuvant is being tested. Phase II trials included 661 adults aged 40-75 years. Subjects had seroconversion rates of 97% for toxin A and 92% for toxin B and no safety issues.[17] The phase III study started in 2013 and is scheduled to be completed December 2017, with an estimated enrollment of 15,000 participants.

Phase II vaccine: VLA84

In July 2016, Valneva Austria announced the completion of phase II trials for a *C. difficile* primary prevention vaccine—VLA84. VLA84 is a recombinant fusion protein of toxin A and B binding regions. The phase II trial was a randomized placebo-controlled study with 500 subjects, and it sought to confirm safety, optimal dose, and formulation for seroconversion (NCT02316470). Similar to the Sanofi product, the intramuscular vaccine has a 3-dose schedule on days 0, 7, and 28. Data analysis included responder rates stratified by age group (50-64 and ≥65 years), but have not been made available to the public yet. A phase III trial of VLA84 is being planned.[18]

Phase III: 3-dose CDI vaccine

A genetically modified and chemically treated recombinant full-length *C. difficile* toxin A and toxin B vaccine by Pfizer completed the first of 2 phase II trials in patients 50-85 years of age (NCT02117570), and participants for the phase III trial are being recruited (NCT03090191). The current ongoing phase II study is evaluating an accelerated and a nonaccelerated intramuscular dosing schedule of this 3-dose CDI vaccine, expected to be completed in 2017 (NCT02561195). The phase II trials exclude patients with a prior or suspected episode of CDI. The randomized parallel assignment with a placebo comparator includes healthy adults aged 65-85 years. The primary outcomes are antibody levels for the treatment arms varying by dose and schedule (accelerated and nonaccelerated schedule; nonaccelerated days 1, 8, 30; accelerated schedule not provided on https://clinicaltrials.gov). The Pfizer vaccine received Fast Track designation from the U.S. Food and Drug Administration in 2014.[19] Positive antibody response occurred in the phase II preplanned interim results, which supported the commencement of the phase III trial in 2017.[20] The phase III trial includes subjects with systemic exposure to antibiotics in the previous 12 weeks, or those with an increased risk of future health care exposure. Subjects with prior CDI, HIV, or any condition or treatment with frequent diarrhea and potential inability to respond to vaccination are excluded (including but not limited to metastatic malignancy, end-stage renal disease, life expectancy <12 months, and congenital or acquired immunodeficiency).

Concerns, limitations, and recommendations for use

Phase III CDI vaccine trials are currently ongoing, and efficacy data are not yet available for any of these products. Efficacy data will be needed to identify associations between patient characteristics and CDI prevention secondary to vaccine administration. Although incomplete inactivation is theoretically possible with the formalin-activated preparations (Cdiffense), the recombinant products eliminate this theoretical risk.

As CDI risk increases substantially in patients age 65 years and older, the vaccine is likely to have the most benefit in an older population in the United States.[21] Analysis of efficacy data by age group (eg, 50-65 years, >65 years) may best direct recommended use given that seroconversion may diminish with age. The VLA84 phase II study included a responder rate analysis stratified for patients age 50-64 years and older than 65 years.

Inclusion criteria for the Sanofi and Pfizer phase III trials differ slightly. Sanofi's Cdiffense trial evaluates only patients with CDI risk factors; therefore, no benefit can be determined for patients older than 50 years without CDI risk factors, including recent or planned hospitalizations and systemic antibiotic exposure. However, Pfizer's phase III trial also includes patients with increased risk of future health care system contact.

The trial inclusion criteria regarding time frame of recent antibiotic exposure varies between the Pfizer vaccine candidate (12 weeks before enrollment) and the Sanofi candidate (12 months before enrollment during a hospitalization). The Sanofi inclusion criteria of planned hospitalization for surgery may provide the most specific patient group for indication. Although surgical prophylactic antibiotic use should be limited in duration, risk for CDI still exists.

Patients with inflammatory bowel disease or previous CDI were excluded from the Sanofi NCT01887912 phase III trial. Without additional subpopulation studies, Cdiffense vaccine will likely not be indicated for patients with inflammatory bowel disease, and this population may remain at risk for worse outcomes. Similarly, other high-risk populations for CDI have been excluded from both ongoing phase III trials. Vaccine benefit initially may be unknown in patients younger than 50 years but with

other risk factors. Additional vaccine studies in at-risk populations will be needed, especially in patients with immunocompromising conditions with increased risk of poor outcomes and potentially impaired vaccine immune response. In addition, an evaluation of the need for boosting will likely be necessary.

Implications for pharmacists

Any CDI primary prevention vaccine approved will likely have a 3-dose schedule and initially be indicated for patients age 50 years and older and at risk for CDI. Pharmacists can play an important role in identifying patients indicated for the vaccine based on the presence of risk factors. In addition, pharmacists may be instrumental in reaching a high vaccination rate for patients at risk for CDI, similar to achievements in pneumococcal and influenza rates.

Although the cost of a CDI vaccine, if approved, is unknown at present, CDI vaccination is expected to be a cost-effective intervention. An effective CDI vaccine could reduce the incidence of costly hospitalizations and patient morbidity. If a CDI vaccine is approved, it will provide primary prevention for the targeted population of the leading cause of health care–associated infection in the United States. Identifying eligible patients for primary prevention will be essential, and pharmacist involvement could meet this need.

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Laurel M. Legenza, PharmD, MS, Comparative Health Systems Global Pharmacy Fellow, School of Pharmacy, University of Wisconsin–Madison, Madison, WI

Susanne G. Barnett, PharmD, Associate Professor (CHS), School of Pharmacy, University of Wisconsin–Madison, Madison, WI

Warren E. Rose, PharmD, MPH, Associate Professor (CHS), School of Pharmacy, University of Wisconsin–Madison, Madison, WI

Appendix B: CDI data collection form

CDI Data Collection Form

Section 1: Demographics & CDI Risk Factors

1. Patient CDI Project Code Number

   _____

2. Hospital of CDI admission (mark only one)
   - ☐ Khaylelitsha Hospital
   - ☐ Ceres Hospital
   - ☐ Paarl Hospital
   - ☐ Stellenbosch hospital
   - ☐ Eerste River Hospital
   - ☐ False Bay Hospital
   - ☐ Groote Schuur Level 3 Hospital
   - ☐ Helderberg Hospital
   - ☐ Karl Bremer Hospital
   - ☐ Mitchells Plain Hospital
   - ☐ Tygerberg Level 3 Hospital
   - ☐ Victoria Hospital
   - ☐ George Hospital

3. Birthday (ex. 01 January 1990)

   _____

4. Gender (mark only one)
   - ☐ Male
   - ☐ Female
   - ☐ Other: _____

5. Ethnicity (mark only one)
   - ☐ Black
   - ☐ White
   - ☐ Coloured
   - ☐ Asian
   - ☐ Unknown
   - ☐ Other: _____

6. Antimicrobial Allergies
   - ☐ "No known drug allergies" (NKDA) documented
   - ☐ Unknown – not documented
   - ☐ Penicillin (PCN)
   - ☐ Sulfa
   - ☐ Other: _____

7. Co-morbid Conditions
   - ☐ HIV (Retroviral disease, RVD)
     - o CD4 Count: _____
   - ☐ Tuberculosis (TB)
   - ☐ Multi-drug-resistant or Extreme-drug-resistant Tuberculosis (MDR-TB and XDR-TB)
   - ☐ Diabetes Type I (insulin-dependent Diabetes)
   - ☐ Diabetes Type II (Diabetes mellites, DM)
   - ☐ Cardiovascular conditions (Heart failure, Hypertension, Hyperlipidemia)
   - ☐ Malignancy (Cancer, Lymphomas, Leukemias)
   - ☐ Inflammatory bowel diseases (IBD): ulcerative colitis (UC), Crohn's
   - ☐ Other immunocompromising condition (e.g. chronic corticosteroid use)
   - ☐ None
   - ☐ Other: _____

8. At home proton-pump inhibitor (PPI) use (e.g. omeprazole, lansoprazole)
   - ☐ Yes
   - ☐ No
   - ☐ Unknown

9. Inpatient proton-pump inhibitor (PPI) use
   - ☐ Yes, but discontinued during CDI treatment
   - ☐ Yes, and continued during CDI treatment
   - ☐ No

10. At home stool softener or laxative use (e.g docusate (Colace))
    - ☐ Yes
    - ☐ No
    - ☐ Unknown

11. Inpatient stool softener or laxative use
    - ☐ Yes, but discontinued during CDI treatment
    - ☐ Yes, and continued during CDI treatment
    - ☐ No

12. At home anti-motility agent use (e.g. loperamide)
    - ☐ Yes
    - ☐ No
    - ☐ Unknown

13. Inpatient anti-motility agent use
    - ☐ Yes, but discontinued during CDI treatment
    - ☐ Yes, and continued during CDI treatment
    - ☐ No

Section 2: CDI Assessment

1. Reason for hospitalization (diagnosis)

_____

2. Symptoms present at admission
   - ☐ Diarrhoea
   - ☐ Blood or pus in stool
   - ☐ Abdominal pain
   - ☐ Nausea/ Vomiting
   - ☐ Rapid heart rate (>100 beats per minute)
   - ☐ Other: _____

3. Total number of days with diarrhoea symptoms prior to admission

_____

4. Documented Diarrhoea (≥3 unformed stools in ≤ 24 hours)
   - ☐ Yes
   - ☐ No

5. Date diarrhoea first documented in folder

_____

6. Diarrhoea and infection severity
   a. Fever >38 C - within 24 hours of day C. diff test is ordered
      - ☐ Yes
      - ☐ No
   b. Blood in diarrhoea - within 24 hours of day C. diff test is ordered
      - ☐ Yes
      - ☐ No
   c. Pseudomembranous colitis (PCM) - anytime in course of CDI
      - ☐ Yes
      - ☐ No
   d. Intensive care unit (ICU) admission during CDI admission
      - ☐ Yes
      - ☐ No
   e. Colectomy
      - ☐ Yes
      - ☐ No
   f. Death - 30-day mortality (from date of CDI test order)
      - ☐ Yes
      - ☐ No

7. Date documenting laboratory stool order from Dr (ex. 01 January 2016)

_____

8. Number of loose stools/day - on date C. diff test is ordered

_____

9. Temperature (max) - within 24 hours of date C. diff test is ordered

_____ ^{o}C

10. Date C. diff test result documented in folder (ex. 01 January 2016)

_____

11. C. diff test result
    - ☐ Positive
    - ☐ Negative
    - ☐ Result not documented

12. Non-CDI treatment antibiotics discontinued after CDI diagnosis
    - ☐ Yes
    - ☐ No
    - ☐ Non-applicable (ex. No other therapy to discontinue)

13. Date non-CDI treatment antibiotics discontinued (ex. 01 January 2016)

_____

14. Rehydration (IV fluids) documented
    - ☐ Yes
    - ☐ No

15. Oral rehydration solution (ORS)
    - ☐ Yes
    - ☐ No

16. "Contact precautions" documented
    - ☐ Yes
    - ☐ No

17. Isolation room
    - ☐ Patient is in isolation room
    - ☐ Isolation room requested
    - ☐ Patient is on the hospital ward without isolation
    - ☐ Unknown if patient in an isolation room

18. Response after 5 days of treatment
    - ☐ Improvement
    - ☐ Failed response after 5 days of treatment

19. Documentation of ID or a specialist consult for CDI
    - ☐ Yes
    - ☐ No

Section 3: Timeline of CDI and Admission

1. Admission date (ex. 01 January 2016)

_____

2. Discharge date (or death) (ex. 01 January 2016)

_____

3. Inhospital mortality
   - ☐ Yes
   - ☐ No

4. Duration of hospitalization (days)

_____

5. Checklist attached
   - ☐ Yes
   - ☐ No

6. Checklist completed
   - ☐ Yes
   - ☐ Partially completed
   - ☐ No

7. Hospital of positive CDI result
   - ☐ Khaylelitsha Hospital
   - ☐ Ceres Hospital
   - ☐ Paarl Hospital
   - ☐ Stellenbosch hospital
   - ☐ Eerste River Hospital
   - ☐ False Bay Hospital
   - ☐ Groote Schuur Level 3 Hospital
   - ☐ Helderberg Hospital
   - ☐ Karl Bremer Hospital
   - ☐ Mitchells Plain Hospital
   - ☐ Tygerberg Level 3 Hospital
   - ☐ Victoria Hospital
   - ☐ George Hospital

8. Colectomy date (ex. 01 January 2016)

_____

9. CDI history
   - ☐ Current CDI episode in chart review is the patient's FIRST (initial) episode of CDI.
   - ☐ Current CDI episode is a recurrence. i.e. The patient has had CDI before.
   - ☐ No documentation of prior CDI. Unknown if this is the first or recurrent episode of CDI.

10. Previous CDI positive result within the last year
    - ☐ Yes
    - ☐ No
    - ☐ Unknown

11. Hospitalized 90 days prior to admission
    - ☐ No
    - ☐ Yes, but no CDI symptoms
    - ☐ Yes, with documented CDI symptoms
    - ☐ Yes, with CDI and did receive CDI treatment
    - ☐ Yes, with CDI and did not receive CDI treatment

12. Hospitalized 30 days prior to admission
    - ☐ No
    - ☐ Yes, but no CDI symptoms
    - ☐ Yes, with documented CDI symptoms
    - ☐ Yes, with CDI and did receive CDI treatment
    - ☐ Yes, with CDI and did not receive CDI treatment

Section 4: Laboratory Markers

1. Haemoglobin (Hb)

_____

2. White blood cell count (WCC)

_____

3. Albumin

_____

4. Baseline serum creatinine (SCr) if documented

_____

5. Serum creatining (SCr)- within 24 hours of C. diff lab test result

_____

6. C-reactive protein (CRP)

_____

Section 5: CDI Treatment

1. CDI Antibiotic treatment during CDI admission
   - ☐ Metronidazole
   - ☐ Vancomycin
   - ☐ Metronidazole AND Vancomycin
   - ☐ None
   - ☐ Other: _____

2. CDI antibiotic strength "mg"

   _____

3. CDI antibiotic route
   - ☐ Oral (PO)
   - ☐ Intravenous (IV)
   - ☐ Rectal

4. CDI antibiotic frequency
   - ☐ Once daily (OD)
   - ☐ Twice daily (BD)
   - ☐ Three times daily (TD/ every 8 hours/ Q8h)
   - ☐ Four times daily (QID/ every 6 hours/ Q6h)

5. Duration of therapy (days) ordered

   _____

6. Antibiotic treatment start date (mm/dd/yyyy)

   _____

7. Treatment stop date (mm/dd/yyyy)

   _____

8. Treatment completed during hospitalization
   - ☐ Yes
   - ☐ No

9. Number CDI doses to be administered while hospitalized

   _____

10. Number of missed CDI therapy doses while hospitalized

    _____

11. Changes to CDI treatment (ex. Change in dose, drug or frequency). Please describe:

    _____

12. Documented health education given to patient
    - ☐ Yes
      - ○ Hand-written notes about health education: _____
    - ☐ No

SECOND CDI Treatment

1. SECOND CDI Antibiotic treatment during CDI admission
   - ☐ Metronidazole
   - ☐ Vancomycin
   - ☐ Metronidazole AND Vancomycin
   - ☐ None
   - ☐ Other: _____

2. CDI antibiotic strength "mg"

   _____

3. CDI antibiotic route
   - ☐ Oral (PO)
   - ☐ Intravenous (IV)
   - ☐ Rectal

4. CDI antibiotic frequency
   - ☐ Once daily (OD)
   - ☐ Twice daily (BD)
   - ☐ Three times daily (TD/ every 8 hours/ Q8h)
   - ☐ Four times daily (QID/ every 6 hours/ Q6h)

5. Duration of therapy (days) ordered

   _____

6. Treatment completed during hospitalization
   - ☐ Yes
   - ☐ No

7. Number CDI doses to be administered while hospitalized

   _____

8. Number of missed CDI therapy doses while hospitalized

   _____

9. Changes to CDI treatment (ex. Change in dose, drug or frequency). Please describe:

   _____

Section 6: Antibiotic Exposure

1. What other antibiotics- past 30 days
   - ☐ None
   - ☐ Penicillin (e.g. PCN, Amoxicillin, etc.)
   - ☐ Quinolone (e.g. Cipro-/Levo-/Moxi-floxacin)
   - ☐ Carbapenems (e.g. Meropenem)
   - ☐ Cephalosporins (e.g. Ceftazidime, Ceftriaxone, Cefazolin, Cefepime, Cefotaxime)
   - ☐ Clindamycin
2. Indications of non-CDI antibiotics (list antibiotics and indications)

   _____
3. What other antibiotics- past 31-90 days
   - ☐ None
   - ☐ Penicillin
   - ☐ Quinolone
   - ☐ Carbapenems
   - ☐ Cephalosporins
   - ☐ Clindamycin
4. Total number of consecutive days on antibiotic therapy prior to CDI test order

   _____
5. Other comments on prior antibiotic exposure or CDI disease or treatment courser treatment course.
   Please summarize shortly if you feel this CDI test was appropriate or not and why

Appendix C: CDI data collection instructions manual

CDI Data Collection Instructions Manual

Project Overview

The objective of this project is to implement a Quality Improvement (QI) checklist to improve the diagnosis and treatment of *Clostridium difficile infection* (CDI) in public sector hospitals in Cape Town. We will try to establish baseline practices through a retrospective data analysis of CDI cases from 2015.

The QI checklist will be implemented in September 2016 and will be studied for one year. We will have access to patients' folders who are treated for CDI in public sector hospitals. This information will continuously be collected and analyzed throughout the year, compared to baseline data, and assessed for post-implementation changes.

Your Role

Your role in this project is to evaluate the information in patients' folders and to document important information into the CDI Data Collection Form (a Google Form). It is important to accurately record as much information from the folders as possible because this will be used to evaluate the successes and limitations of the checklist, as well as help determine what changes should be made.

CDI Data Collection Form

In addition to the printed version of the data collection questions, an online form has been created to assist you in recording the most important information from the patients' folders. The data collection form is split into six sections (Demographics, CDI Assessment, Timeline of CDI and Admission, Laboratory Markers, CDI Treatment, and Antibiotic Exposure) with a varying number of questions in each section.

Some questions may not pertain to every patient, and some folders will not have the documented information necessary to answer all the questions. If this is the case, leave that question blank. Many of the questions were formulated based on CDI treatment guidelines (see below), but we acknowledge this information may not be documented or may be hard to find. Part of the project is assessing the baseline standard of care and common CDI treatment practices in each of the hospitals.

If you have thoroughly looked through the entire patient folder and cannot find the answer to a question from the data collection form, it is OK to leave that question blank. In order to further explain on the questions from the data collection form, each question is outline and further described below. These explanations include:

- **Clarification** for ambiguous questions and/or further defining terms in the question
- **Importance** of each question and why that information is necessary to be collected. It may be helpful to read South Africa's CDI guidelines (included on the next pages) to gain further understanding of the importance of these questions.
- **Location** in the patient folder where you might be able to find the answer to the question

****It is important to understand that all patient charts will be different. This manual is meant to help you, but it does not contain all the answers for every unique patient folder that we will come across.**

Tips

1. Read through and familiarize yourself with the contents of the data collection form.
2. Read through the entire folder and Inpatient Prescription Charts in chronological order to gain the best understanding of the patient's clinical situation.
    a. The answers to some questions may be located in multiple different locations throughout the folder, so it is important to read through the whole folder once before answering any questions. This way, it is assured that each question is answered *fully* and *accurately.*
    b. If you are familiar with the questions from the data collection form, you can mark where the information is in the folder to make it easier to re-locate and record answers into the data collection form.
    c. There may be many Inpatient Prescription Chart booklets, so make sure you read the dates carefully.
3. Don't get caught up on terms you don't understand—they will often come back up or reveal their significance later in the charts

STANDARD TREATMENT GUIDELINES AND ESSENTIAL MEDICINES LIST FOR SOUTH AFRICA (2015)

1.3.4 DIARRHOEA, ANTIBIOTIC-ASSOCIATED

DESCRIPTION

Diarrhoea caused by altered bowel flora due to antibiotic exposure. Clostridium difficile infection may result in severe disease and/or the development of pseudomembranous colitis. Diagnosis is confirmed in the laboratory on a stool sample.

GENERAL MEASURES

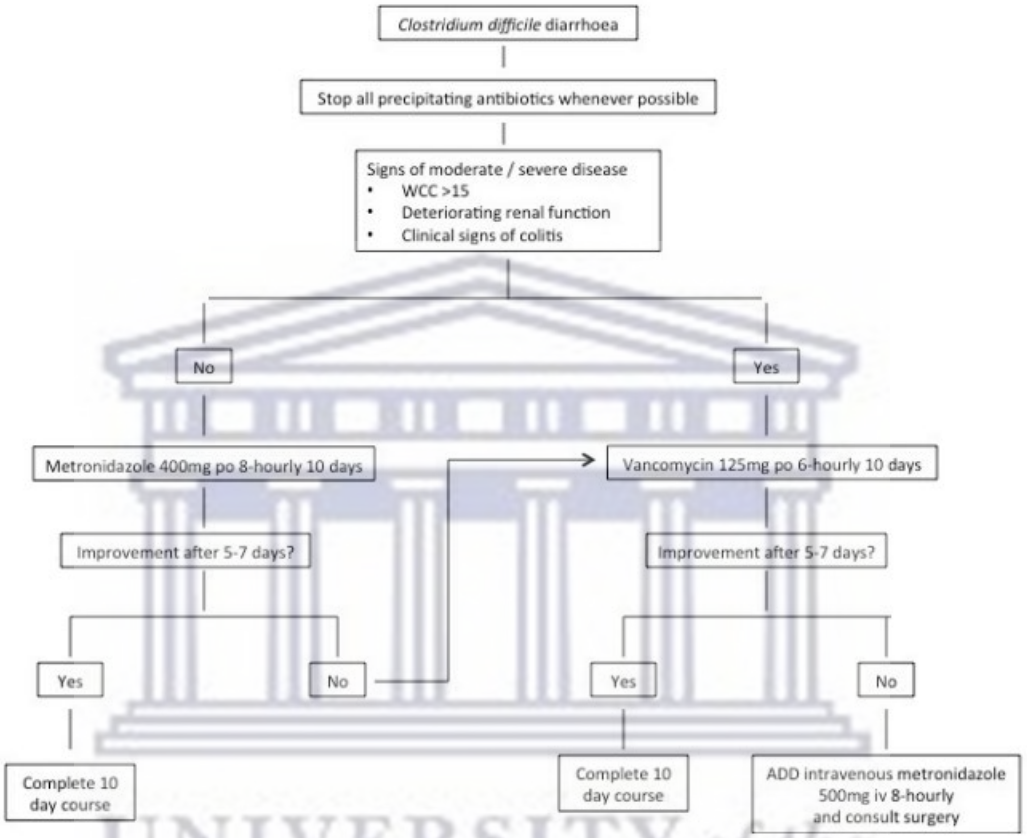
The most important aspect of management is discontinuing antibiotics. Rehydration may be necessary. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated. Surgery for bowel perforation.

MEDICINE TREATMENT

- Loperamide is contraindicated as it may result in toxic megacolon.
- If diarrhoea does not settle on antibiotic withdrawal or if pseudomembranous colitis is present:
    - Metronidazole, oral, 400 mg 8 hourly for 10 days
- Failure to respond to metronidazole after 5 days - consult a specialist and:
    - ADD: Vancomycin, oral, 125 mg 6 hourly. (Give the parenteral formulation orally).

SOUTH AFRICAN ANTIBIOTIC STEWARDSHIP PROGRAMME (SAASP)
GUIDE TO ANTIBIOTIC PRESCRIBING

Management of *C. difficile* diarrhoea



CDI Data Collection Form Contents

**NOTE: Each hyperlink below will take you to its' respective explanation so you do not have to continuously scroll through all the questions. In addition, each explanation has a hyperlink ("Back to Contents") that will bring you back to this page so you can easily continue to follow along as you complete the data collection form.

6. Checklist completed
7. Hospital of positive CDI result
8. Colectomy date
9. CDI history
10. Previous CDI positive result within the last year
11. Hospitalized 90 days prior to admission
12. Hospitalized 30 days prior to admission

D. Laboratory Markers
1. Haemoglobin (Hb)
2. White blood cell count (WBC)
3. Albumin
4. Baseline serum creatinine (SCr) if documented
5. Serum creatinine (SCr) - within 24 hours of C. diff lab test result
6. C-reactive protein (CRP)

E. CDI Treatment
1. CDI Antibiotic treatment during CDI admission
2. CDI antibiotic strength "mg"
3. CDI antibiotic route
4. CDI antibiotic frequency
5. Duration of therapy (days) ordered
6. Treatment completed during hospitalization
7. Number CDI doses to be administered while hospitalized
8. Number of missed CDI therapy doses while hospitalized
9. Were there any changes to the CDI treatment?
10. Documented health education given to patient

F. Antibiotic Exposure
1. What other antibiotics- past 30 days
2. Indications of non-CDI antibiotics (list antibiotics and indications)
3. What other antibiotics- past 31-90 days
4. Total number of consecutive days on antibiotic therapy prior to CDI test order
5. Other comments on prior antibiotic exposure or CDI disease or treatment course

A. Demographics

Importance

- Demographic information is important to collect and document so we can understand the entire patient case. Some demographic characteristics can cause patients to be at an increased (or decreased) risk of CDI.

Location

- Demographic information will be located on the first few pages of the patient folder.

---

1. Patient CDI Project Code Number

Location

See key for included patients and their number coded from national identifier

Top

---

2. Hospital of CDI admission

Clarification

- Patients may switch hospitals during the course of their admission, but this question is asking which hospital the patient was originally admitted at.

Top

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3. Birthday
4. Gender
5. Ethnicity

Clarification

- Ethnicity is rarely documented in patient charts, but sometimes the patient's photo identification is included in the chart. If race can be deduced from the photo ID, include race in the data collection form, but if race cannot be identified leave this blank.

Importance

- Age is an important risk factor for CDI. Gender and ethnicity may play a role in CDI that is not currently understood.

Top

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6. Antimicrobial Allergies

Clarification

- You probably won't find much more than Penicillin or Sulfa documented for allergies. If there are other allergies listed, document that in the fill-in "Other" section.
- It is not important to record the type of reaction (e.g. rash, anaphylaxis, etc.)

Importance

- Allergies can influence CDI treatment decisions.

Top

7. Co-morbid Conditions

Clarification

- It is not necessary to record all the patient's medications for co-morbid conditions

a. HIV
   - also referred to as retroviral disease (RVD)
   - Record CD4+ cell count as a measure of the patient's current immunosuppression

b. Tuberculosis (TB)

c. Multi-drug-resistant or Extreme-drug-resistant Tuberculosis (MDR-TB and XDR-TB)
   - The patient folders will probably just say MDR-TB or XDR-TB

d. Diabetes Type I (insulin-dependent Diabetes)

e. Diabetes Type II (Diabetes mellites, DM)

f. Cardiovascular conditions (Heart failure, Hypertension, Hyperlipidemia)
   - Other cardiovascular conditions may be noted as:
     1. Cardiovascular disease (CVD)
     2. Chronic heart failure (CHF)
     3. Hypertension/ High blood pressure (HTN)
     4. Hyperlipidemia/ High cholesterol
     5. History of stroke/ heart attack/ arrhythmia
     6. Other heart valve conditions/ complications

g. Malignancy (Cancer, Lymphomas, Leukemias)
   - Most forms of cancer will be labeled as cancer (i.e. lung cancer, breast cancer, etc.)
   - Blood cancers are the exceptions as they will be called *lymphoma* or *leukemia*. There are many different types of lymphoma and leukemia including:
     1. Non-Hodgkin lymphoma
     2. Hodgkin lymphoma
     3. Multiple myeloma (MM)
     4. Acute lymphobloastic/ myeloid leukemia (ALL/ AML)
     5. Chronic lymphocytic/ myeloid leukemia (CLL/ CML)

h. Inflammatory bowel diseases (IBD):
   - Types of IBD include:
     1. Ulcerative colitis (UC)
     2. Crohn's

i. Other immunocompromising condition
   - Long-term corticosteroid use (often with transplant patients)

j. None

k. Other
   - List any other chronic conditions or conditions that you believe may influence the patient's CDI risk or treatment

Top

Questions 8-10:

Clarification

- Each of these questions will assess medication use *before* the patient was admitted to the hospital (at home) and *after* the patient was admitted (inpatient)
- Home medications are often not documented, so if there is no mention of whether or not the medication was used at home before admission, mark "unknown"

8. At home proton-pump inhibitor (PPI) use (e.g. Omeprazole, Lansoprazole)

9. Inpatient proton-pump inhibitor (PPI) use

Clarification

- Five PPIs are available in South Africa: omeprazole, lansoprazole, esomeprazole, rabeprazole, and pantoprazole. (Only **omeprazole** and **lansoprazole** will be used in public sector hospitals)

Importance

- Proton-pump inhibitors (PPIs) are a class of medications that work by inhibiting the secretion of gastric acid into the stomach. Literature has shown a link between the use of PPIs and CDI, which is probably due to disruption of the normal GI flora. PPIs can also increase a patient's risk of CDI relapse and recurrence.

Top

10. At home stool softener or laxative use (e.g. docusate (Colace))

11. Inpatient stool softener or laxative use

Clarification

- There are many types of stool softeners and laxatives available. Below are some of the common classes and commonly used medications in each class. There may be other products used that are not on this list, but please do still document those.
- Record use on the day of the CDI test (or surrounding 48 hours) AND indicate if the agent was continued during CDI treatment (same for anti-motility agents)

Stool softeners	Docusate (Colace)
Bulk-forming	Metamucil (Psyllium, Konsyl, Serutan) Methylcellulose
Stimulants	Senna (Senokot, SennaLax) Bisacodyl (Dulcolax, Correctol) Castor oil (Purge)
Saline Laxatives	Milk of Magnesia Haley's MO (magnesium hydroxide)

Importance

- The use of stool softeners and laxatives may contribute to CDI.

Top

12. At home anti-motility agent use (e.g. loperamide)

13. Inpatient anti-motility agent use (e.g. loperamide)

Clarification

- Anti-motility agents like loperamide (Imodium) are used to treat diarrhea, but can mask the signs of CDI

Importance

- These agents are contraindicated during CDI treatment due to the risk of toxic megacolon

Top

B. CDI Assessment

Importance

- This section will assess the patient's initial presentation to the hospital and subsequent course of CDI. Many of these questions were formulated based on the treatment guidelines.

---

1. Reason for hospitalization (diagnosis)

Clarification

- This question is asking for the *primary reason* the patient was admitted to the hospital.

Importance

- Some patients will present to the hospital with CDI, but others will develop CDI during their hospital stay. The timing of CDI symptoms is important to determine cause and appropriate treatment.

Location

- Reason for hospitalization can be found on the first page in the patient folder under "Presenting Problem" and "Associated Complaints".
- Many patients will have multiple presenting problems and complaints, but doctors will most often prioritize the problems in these sections.

Top

---

2. Symptoms present at admission

Clarification

- This section is looking to capture all symptoms presented by the patient at admission, whether or not they are related to CDI. CDI symptoms will be listed on the Google Form, but write in any other symptoms in the "Other" line.

Importance

- Many patients are admitted to the hospital without a clear diagnosis, so this question can be used to identify possible CDI symptoms and gain a more complete picture of what brought the patient to the hospital in the first place.

Location:

- Many of the admission symptoms will be noted in the "Presenting Problem" or "Associated Complaints" sections, but they may be located throughout the initial assessment pages.

Top

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3. Total number of days with diarrhoea symptoms prior to admission

Clarification

- This question aims to determine how long the patient has been experiencing diarrhoea prior to admission. This question is only relevant for patients who presented to the hospital with diarrhoea.
- Duration of diarrhoea can help guide CDI diagnosis and treatment.

Location

- This information will be found in the ER or admitting notes.

Top

---

4. Documented diarrhoea (≥3 unformed stools in ≤24 hours)

Clarification

- This question was formulated based on the CDI treatment guidelines, but this information may not always be documented in patient folders.

Importance

- Diarrhoea is defined as the presence of 3 or more unformed stools (taking the form of its container) in less than 24 hours. This information can help determine if a patient was appropriately diagnosed

Location

- If documented, this information will be found in the nursing notes or less frequently in the doctor's notes. Start at the day diarrhoea presented and read up until the CDI test order.

Top

---

5. Date diarrhoea first documented in folder

Clarification

- If the patient initially presented to the hospital with diarrhoea, this date will be the same as the admission date.
- If the patient developed CDI while in the hospital, read through the chart in a chronological order to find the first mention of diarrhoea and use that date.

Importance

- The presence of diarrhoea is the first cue in ordering a C. diff stool test, which begins the diagnosis and treatment process.

Top

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6. Diarrhoea and infection severity

a) Fever >38 C – within 24 hours of day C. diff test is ordered
b) Blood in diarrhoea – within 24 hours day C. diff test is ordered
c) Pseudomembranous colitis (PCM) - anytime in course of CDI
d) Intensive care unit (ICU) admission during CDI admission
e) Colectomy
f) Death - 30-day mortality (from date of CDI test order)

Importance

- The severity of diarrhoea and infection markers can help diagnose CDI and determine appropriate treatment.

Location

- If documented, this information will be found in the clinical notes. Fever charts will be documented on a separate sheet in the results and/or nursing documents.

Top

---

7. Date documenting laboratory stool order from Doctor

Clarification

- May be referred to as "Stool MCS" (MCS= microscopy, culture, and sensitivity)

Importance

- The date on which the doctor ordered the stool helps to determine the timeline of CDI diagnosis and treatment.

Location

- This will be found in the doctor notes and/or on the medication blue board in the doctor's notes to the nurses.

Top

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8. Number of loose stools per day - on date C. diff test is ordered

Location

- If this information is available, it will be documented either in the clinical notes OR in the nursing progress notes from the same day the stool test was ordered

Top

---

9. Temperature (max) – within 24 hours of date C. diff test is ordered

Clarification

- Temperatures may be measured multiple times per day, so this question is just looking for the highest recorded temperature within 24 hours of when the doctor ordered the C. diff test.
    - This is looking for the highest temperature that occurs within +/- 24 hours the C. diff test (48-hour window)
- Temperature will be measured in degrees Celsius (°C)

Location

- One of the pages in the folder will be a graph of the patient's measured temperature during their hospital stay. The graph should allow you to determine the patient's temperature to the closest tenth (0.1) of a degree.
- Use the temperature recorded closest to the time when the doctor ordered the C. diff test (this may be before the test was ordered)

Top

---

10. Date C. diff test result documented in folder

Importance

- The date on which the test result is documented helps to determine the timeline of CDI diagnosis and treatment.
- If a patient has multiple CDI positive test results, treat each positive test as a separate encounter (e.g. complete a separate Google form for each)
    *** UNLESS the tests are within 48 hours of each other, then only use the first test and disregard the second.

Top

---

11. C. diff test result

Clarification

- If it doesn't explicitly say the result of the C. diff test result, but it is clear they started treatment mark "Result not documented"

Top

---

12. Non-CDI treatment antibiotics discontinued after CDI diagnosis

Clarification

- Non-CDI antibiotics are all antibiotics except Metronidazole (Flagyl) and Vancomycin

Importance

- The use of non-CDI antibiotics can cause and/or worsen CDI
- Per the guidelines, all non-CDI antibiotics should be discontinued upon CDI diagnosis

Location

- Inpatient Prescription Chart

Top

---

13. Date non-CDI treatment antibiotics discontinued

Clarification

- This question only pertains if you answered "yes" to previous question.

Location

- Inpatient Prescription Chart

Top

---

14. Rehydration (IV fluids) documented

15. Oral rehydration solution (ORS)

Importance

- Patients with CDI can become very dehydrated due to excessive fluid loss. These patients may be given intravenous or oral rehydration therapy.

Location

- IV and oral rehydration fluids may be documented in the medication blue board, doctor's clinical notes, or the ER admission notes.

Top

---

16. "Contact precautions" documented

Importance

- Contact precautions are recommended by the SAASP, but current practices will be facility specific.

Location

- Will state "Contact Precautions" somewhere in chart, probably near the time the C. diff test result was ordered and/or came back positive.

Top

---

17. Isolation room

Location

- A request for an isolation room will be notated in the clinical notes and/or the medication blude board.

Top

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18. Response after 5 days of treatment

Clarification

- Clinical response can be determined by improvements in fever, white cell count (WCC), renal function, and/or diarrhoea frequency.
- "5 days" is part of the guidelines, but we are really looking for any clinical signs of improvement within the first 5 days (+/- 24 hours)

Importance

- Per the CDI South African treatment guidelines, any patient who is not clinically improving after 5 days of treatment should receive treatment escalation and be re-evaluated by a specialist.

Location

- This may be stated in the notes with something along the lines of, "Patient improving"
- If there is no documentation of the patients' response to treatment, use the lab values and fever chart to see if the patients' vitals and labs improved within this timeframe.

Top

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19. Documentation of ID or a specialist consult for CDI

Importance

- Per the CDI South African treatment guidelines, any patient who is not clinically improving after 5 days of treatment should receive treatment escalation and be re-evaluated by a specialist.

Top

C. Timeline of CDI and Admission

Importance:

- Once CDI has been diagnosed, it is crucial to start treatment as early as possible to achieve optimal patient outcomes. This section aims to create a timeline of the patients' current and past episodes of CDI.

---

1. Admission date

Clarification

- If the patient did not initially present with diarrhoea or CDI (i.e. the patient developed CDI in the hospital), use the initial hospital admission date.
- If a patient has multiple CDI positive test results, treat each positive test as a separate encounter (e.g. complete a separate Google form for each)
    - *** UNLESS the tests are within 48 hours of each other, then only use the first test and disregard the second
    - This may mean that some patients have multiple Google forms with the same admission date but different test result dates

Location

- Use the date on the very first page of the patient folder.

Top

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2. Discharge date (or death)

Location

- For discharge, use the last date in the patient's folder.
- For death, use date in the folder where the patient's death was first mentioned.

Top

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3. Inhospital mortality

Clarification

- It should be clear from the last few notes in the folder whether or not the patient died or is discharging from the hospital and going home.
- This will be used to determine if the date from the previous question was a discharge date or date of death.

Location

- Death will be noted at the end of the doctor's notes as well as the Declaration of Death form in the patient's folder.

Top

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4. Duration of hospitalization (days)

Location

- Count the days in between the admission date (on the first page in the folder) and the discharge date (last page in the folder) to determine the how many days the patient was in the hospital

Top

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5. Checklist attached

6. Checklist completed

Clarification

- Checklist may be included post-intervention (not expected to be included pre-intervention)

Top

---

7. Hospital of positive CDI result

Clarification

- CDI treatment usually lasts 10-14 days.
  - Many patients will remain hospitalized longer than this and receive the full course of treatment while in the hospital.
  - Other patients will discharge early and be responsible for taking their antibiotics at home.

Location

- Top of the patient charts

Top

---

8. Colectomy date

Location

- This information may be located in the clinical notes and/or surgery notes.

Top

---

9. CDI history

a) Current CDI episode in chart review is the patient's FIRST (initial) episode of CDI.
b) Current CDI episode is a recurrence. i.e. The patient has had CDI before.
c) No documentation of prior CDI. Unknown if this is the first or recurrent episode of CDI.

Clarification

- We would ideally like to know this information, but it may not be documented.

Importance

- Previous episodes of CDI put patient at risk of CDI relapse or recurrence.

Location

- Past medical history may or may not be documented in the initial assessment upon admission.
- If there is a history of CDI, it may be mentioned in the assessment or plan notes prior to the CDI diagnosis.

Top

---

10. Previous CDI positive result within the last year

Clarification

- This information will probably be hard to find, but it may be mentioned in some of the notes.

Top

---

11. Hospitalized 90 days prior to admission

Clarification

- This question is aiming to see if any patients with CDI are being missed during CDI screening during past hospitalizations.

Importance

- Hospitalization, CDI episodes and/or CDI treatment in the past 90 days may increase a patient's risk of developing CDI

Top

---

12. Hospitalized 30 days prior to admission

Clarification

- This question is aiming to see if any patients with CDI are being missed during CDI screening during past hospitalizations.

Importance

- Hospitalization, CDI episodes and/or CDI treatment in the past 30 days may increase a patient's risk of developing CDI

Location

- This information can be found in previous medical documents in the patient's folder and/or from the doctor's notes.

Top

D. Laboratory Markers

Location

- All laboratory values can be located on the "Results Sheet". Use the values located in this chart rather than lab values that are noted throughout the patient chart, unless a lab value can be found in the chart but not the results table.
- If available, collect laboratory values for the **24 hours before OR after the CDI test** (day of, before, or day after the test)
- If a lab value is not recorded, leave that question blank.

---

1. Haemoglobin (Hb)

Clarification

- protein in a blood that carries oxygen
  - measure of anemia
- Normal range for men ~ 13.8-17.2 g/dL
- Normal range for women ~ 12.1-15.1 g/dL

Top

---

2. White blood cell count (WCC)

Clarification

- also known as leukocytes
  - help fight infections
- Normal range is 4,500-11,000 cells/mcL

Top

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3. Albumin

Clarification

- protein made in the liver
  - can evaluate kidney function
  - can help evaluate a patients general health status
- Normal range is 3.4-5.4 g/dL

Top

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4. Baseline serum creatinine (SCr)

Clarification

- measure of how well the kidney is working
- "Normal" ranges vary from patient to patient.
    - Knowing patient's baseline SCr value can help providers determine how much damage has occurred to the kidneys.

Top

---

5. Serum creatinine (SCr)- - within 24 hours of C. diff lab test result

Clarification

- measure of how well the patient's kidney is working at the time of CDI. This can help with evaluate infection severity and can guide treatment selection.
- This is looking for the patient's serum creatinine levels +/- 24 hours of the C. diff lab test result (48-hour window)
    - If a serum creatinine is not recorded within +/- 24 hours of the C. diff lab test result, leave the answer blank

Top

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6. C-reactive protein (CRP)

Clarification

- protein made in the liver. CRP levels rise when there a patient is experiencing inflammation.
- Normally, there should not be any CRP in the blood.
- Patients with CRP levels above 1.0mg/L may be at increased risk for cardiovascular disease

Top

E. CDI Treatment

Clarification

- This section aims to determine exactly what treatment each patient received and for how long.

Importance

- Quick and appropriate treatment is crucial for the treatment of CDI.
- Sub-therapeutic treatment doses or duration can cause CDI relapse and/or recurrence.

Location

- All these questions should be available from the Inpatient Prescription Charts
- There may be multiple Inpatient Prescription Charts that contain one single course of treatment, so make sure you read all the Inpatient Prescription Charts chronologically and carefully.

---

1. CDI Antibiotic treatment during CDI admission

Clarification

- CDI is treated with either Metronidazole (Flagyl) 400mg TD and/or Vancomycin 125mg QID for 10-14 days.

Top

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2. CDI antibiotic strength "mg"

Importance

- It is important the correct strength of medication is used to adequately eradicate the infection.

Top

---

3. CDI antibiotic route

Clarification

- Common medication routes include oral (PO), intravenously (IV), intramuscularly (IM), and subcutaneous (SQ)

Top

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4. CDI antibiotic frequency

Clarification

- Once daily = OD, dly
- Twice daily = BD
- Three times daily = TD
- Four times daily = every 6 hours

Top

---

5. Duration of therapy (days) ordered

Clarification

- Ideally, treatment duration would be notated upon the start of CDI treatment

Location

- Look in the plan notes, but this may not always be documented.

Top

---

6. Treatment completed during hospitalization

Clarification

- CDI treatment usually lasts 10-14 days.

Importance

- Many patients will remain hospitalized longer than this and receive the full course of treatment while in the hospital. Other patients may discharge early and finish their antibiotic treatment at home. These patients are at risk of relapse if they don't take their antibiotics as directed.

Location

- Look at the Inpatient Prescription Charts to determine how many days of treatment were given in the hospital. Compare that to the documented length of treatment (probably found somewhere in the plan)

Top

---

7. Number CDI doses to be administered while hospitalized

Clarification

- Will be the full course of treatment days if the patient remains in the hospital for the entire treatment course.
- If a patient discharges before treatment completion, count the total number of doses administered while the patient was in the hospital (should be less than the total number of doses to be given)

Top

---

8. Number of missed CDI therapy doses while hospitalized

Clarification

- Nurses sign their initials next to any medication dose they administer to patients. You can determine the number of missed doses by looking at the "Inpatient Prescription Chart" and counting the number of boxes/gaps/times when there are no initials in the treatment course

Top

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9. Were there any changes to the CDI treatment?

Clarification

- A change may be made to the CDI treatment for many reasons including :
  - An error was discovered in the previous antibiotic order (i.e. ordering Flagyl BD instead of TD)
  - The patient does not respond to treatment

Top

---

10. Documented health education given to patient

Location

- There is a box in the patient folder titled "Information Given to Patient"
  - In this box, there is a yes/no question about health education
    - There is also an area where notes can be made. If there are notes about the health education given to patients, please record that in the "Other" box

Top

F. Antibiotic Exposure

Clarification

- If a patient developed CDI while in the hospital, it is important to record all antibiotics the patient received before developing CDI. If the patient presented to the hospital with CDI, recent antibiotic exposure may not be available in the charts.

Importance

- Recent antibiotic use is a risk factor for CDI because antibiotics kill the normal bacteria in the gut and allow organisms like C diff. to cause infection. This section is trying to assess patients' recent antibiotic exposure so we can understand what caused the CDI.

Location

- If the patient developed CDI while in the hospital, use the Inpatient Medication Record to find any antibiotics administered prior to CDI diagnosis.

CDI antibiotics:

- Vancomycin
- Metronidazole (Flagyl)

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1. What other antibiotics- past 30 days

a) **Penicillins:** Penicillin G (benzylpenicillin), Oxacillin, Cloxacillin, Flucloxacillin, Piperacillin, Amoxicillin
b) **Quinolones:** Ciprofloxacin, Levofloxacin, Moxifloxacin, Ofloxacin
c) **Carbapenems:** Meropenem
d) **Cephalosporins:** Ceftazidime, Ceftriaxone, Cefazolin, Cefepine, Cefotaxime
e) **Clindamycin**

Clarification

- Some antibiotics carry a higher risk of perpetuating CDI, so this question is trying to assess the patients risk factors as they pertain to past antibiotic exposure.

Top

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2. Indications of non-CDI antibiotics (list antibiotics and indications)

Clarification

- This may be difficult to find if the patient was not treated in patient prior to CDI treatment.
- If the patient has **MDR-TB**: Fluoroquinolones (Levofloxacin, Moxifloxacin, Gatifloxacin) and Aminoglycosides (Streptomycin, amikacin, kanamycin) are used for second-line treatment of MDR and XDR Tuberculosis.

Location

- If the antibiotics were given while in the hospital, you may be able to find an indication in the plan notes for the corresponding dates.

Top

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3. What other antibiotics- past 31-90 days

Location

- May be difficult to find if patient was not inpatient

Top

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4. Total number of consecutive days on antibiotic therapy prior to CDI test order

Location

- Inpatient Prescription Chart

Top

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5. Other comments on prior antibiotic exposure or CDI disease or treatment course

Clarification

- This is an open-ended question where you can add any notes about the patient that you think are important, but were not covered in answers to other questions.

Top

Appendix D: Semi-structured interview guide

Appendix D

Semi-structured interview guide

***C. difficile* infection (CDI) in Cape Town, South Africa**

The semi-structured interviews will be guided by the following themes: 1) facilitators to CDI treatment (ex. identification of CDI, laboratory testing, and receiving medication doses as ordered), 2) barriers to CDI treatment 3) facilitators CDI prevention (ex. Infection control practices), 4) barriers to CDI prevention, 5) opportunities for improvement CDI treatment, and 6) opportunities for preventing CDI. Interviewees will also be shown the example checklist as points for discussion and an opportunity to provide input on the checklist. The patient interviews will ask about their treatment experience and understanding of the disease treatment and prevention precautions.

Semi-Structured Interview Guide

Area I: Background and Contextual Issues

You indicated that your title/position is [_____]. Can you briefly tell me about the responsibilities that this position entails?

- o What are the kinds of tasks that you typically perform from day to day?

What is your involvement in infection control or CDI treatment?

- o Please tell me about any related responsibilities that you have.

Area II: Perceptions of *C. difficile* and the *C. difficile checklist or C. difficile* treatment

Let's focus our discussion now and talk specifically about *C. difficile* infections.

How much of a problem do you think *C. difficile* is in your unit? How much of a problem do you think that leadership at your facility feels that *C. difficile* is in your unit? How important do you feel they think it is?

- o What opportunities are there for leadership and staff to discuss ideas around *C. difficile* prevention in your unit? (collaboration to promote change)
- o What happens if there is a good idea that has potential for sustainable change? Who is involved in promoting change? Does leadership support those changes and promote them?
- o What has been done in your hospital in the past year related to *C. difficile* prevention?
- o How much of a problem do you think the public health system as a whole thinks that *C. difficile* treatment and diagnosis?

Has there ever been an acute *C. difficile* situation or *C. difficile* outbreak in your hospital?

- o Tell me about the situation/outbreak.
- o What did you and your colleagues do? What was your hospital's response?
- o Did you feel that your efforts/response were effective?
- o What happened afterwards?

How familiar would say you are with the steps for *C. difficile* diagnosis and treatment?

POST-CHECKLIST IMPLEMENTATION QUESTIONS

How familiar would say you are with the ***C. difficile* checklist**?

- o What steps have been taken to implement the checklist in your area of work?
- o How did you learn about the checklist? Do you feel that you've been adequately trained in the steps?
- o What components of the checklist are you the most familiar with?

o Are there particular aspects of the checklist that you feel are more important than others? Why do you say that?
What is your perception of the evidence supporting implementation of the *C. difficile* checklist in hospitals? Or just *C. difficile* diagnosis and treatment overall?
o How does research evidence inform that opinion?
o Clinical experience?
o Patient preference?
o Previous data or local data/experiences? (*For example, some facilities may have more of a problem with C. difficile than others, and therefore may have more local data to develop site-specific evidence.*)

What is your perception of **leadership support** of implementation of the *C. difficile* checklist in Your unit? Or *C. difficile* identification and treatment overall?

o What steps has leadership at your facility taken to express support/non-support of the checklist in your unit? Or *C. difficile* identification and treatment overall?
o To what extent is infection control staff at the hospital level involved in preventing *C. difficile*?
o Who has been identified as the leader(s) in your unit regarding *C. difficile* checklist in your unit? Or just *C. difficile* treatment overall?
o What are general staff responsibilities around C. *difficile* treatment in the units?
o In what ways do members of the patient care team share and take responsibility for *C. difficile* prevention, identification, and treatment?
o What does leadership do at your facility to promote innovation or development of best practices to support the *C. difficile* checklist? Or just *C. difficile* treatment overall?

What types of **resources** have been committed to implementation of the C. *difficile* checklist in the units? Or *C. difficile* treatment overall?

o What training has been provided?
o What staff has been committed to it?
o What physical resources or supplies have been committed to it?
o Does your unit have a specific budget committed to this?
o What feedback or data have you been provided regarding implementation of aspects of the *C. difficile* checklist? Or *C. difficile* treatment overall? What goals do you have within your unit regarding the *C. difficile* checklist? Or just *C. difficile* treatment overall?
o What processes are in place to hold people accountable for their practices regarding aspects of the *C. difficile* checklist? Or *C. difficile* treatment overall?

Topic Area III: Current Practices around areas of the guidelines

Questions for health care providers (Physicians/Nurses):

The SAASP Antibiotic Guideline says diagnostic testing for C. difficile infection in patients with acute diarrhea requiring hospitalization or with blood mixed with stool, suspected of having C. difficile infection and recent antibiotic exposure.

- What symptoms is a patient exhibiting if you suspect they have a *C. difficile* infection? Who ultimately makes this determination?
- At what point do you order a *C. difficile* test for patients suspected of having a *C. difficile* infection? Who ultimately makes this determination?

o How do you inform the patient they will be placed on contact isolation? Who informs the patient they are being placed on contact isolation? Are there specific educational materials or topics that are supposed to be covered?
- What process do you use to identify "appropriate diagnostic testing?"
o What type of tests are available (ex. PCR, antibody)?

- How long do you typically have to wait before receiving results of a *C. difficile* test? Does it depend on the type of test given?
- How do you communicate results of the test to the patient? How do you communicate the results to a patient's family or other visitors?
- How do you classify signs of moderate/severe disease? (SAASP Guidelines: WCC>15, deteriorating renal function, clinical signs of colitis)
- Are antibiotics stopped for patients with acute diarrhea? When? *C. difficile*?
- How is the treatment choice of *C. difficile* determined? (Metronidazole vs. Vancomycin)
- How is clinical improvement assessed? (ex. at 5-7 days)
- What happens if a patient is not showing signs of improvement? (ex. change therapy?)

The SAASP Antibiotic Guideline says: "The most important tools to prevent spread of infection are hand hygiene and contact precautions."
- What is the gowning and gloving policy at your facility? Is it upon entry?
- At what point do you discontinue contact precautions for patients whose *C. difficile* infection has cleared?
- In what situations would you keep a patient on contact isolation throughout the duration of their hospitalization?
- In what situations do you use alcohol based solutions for hand decontamination?
- In what situations do you use soap and water for hand decontamination?
- In what situations do you use gloves?
- How do you promote or optimize hand hygiene compliance in your unit?
o Where are hand hygiene stations located? Inside patient room, outside patient room, both?
- How do you monitor hand hygiene compliance on your unit? Who is responsible for monitoring hand hygiene compliance in your unit?
- Do you receive feedback on your own hand hygiene compliance? Do they provide hand hygiene compliance feedback at the unit level? How is this feedback provided to you? How often?

Environment
- What are the barriers to performing hand hygiene when entering a contact isolation room? When leaving a contact isolation room?
- What percentage of the time would you say you perform hand hygiene upon entering a contact isolation room? When leaving one? What prevents you from doing so?
- What could be done to make it easier to perform hand hygiene at the appropriate times?
- What are the barriers to testing for *C. difficile*?
- What are the barriers to initiating treatment?
- Sometimes patients miss doses of medication in the hospital. What are the barriers to patients receiving ordered treatment doses as ordered?

Questions regarding Infection Control and Environmental Services:

Tools

- What cleaning agents, tools or devices, are used in a room that had a *C. difficile* positive patient?
    - o Do you know if this cleaning agent is active against *C. difficile*?
    - o Is bleach used? Hydrogen peroxide vapor? Ultraviolet disinfection?
    - o Are there additional tools you wish the hospital had?
    - o Does the hospital ever have a problem getting supplies?
- What is your facility's policy for cleaning *C. difficile* contact isolation rooms?
    - o Are the rooms/patient space cleaned daily? At discharge only?
    - o How are cleaning personnel informed about which rooms need to be cleaned? In what way is it communicated? Is that communication documented?
    - o Who is responsible for tracking cleaning of the room? How is it tracked?
    - What processes or documentation are in place to document the individual tasks that need to be completed for cleaning a room? Is this list available or is it just memorized by cleaning staff?
    - In what ways do you monitor cleaning practices to ensure they are appropriate?
    - o Direct observations?
    - o Culture surfaces in the room before and after cleaning?
    - o Fluorescent markers (the mark is checked after cleaning to see if it has been removed which would indicate adequate cleaning)?
- How does the layout or organization of the room affect cleaning ability?

Topical Area III: Needs and Practices Related to *C. difficile* treatment

What resources do you think that you need in order to do a good job of treating *C. difficile* in your hospital?

- o Personnel needs
- o Equipment needs
- o Materials

Are there any "best practices" that you personally have for *C. difficile* treatment and *C. difficile* patient care that you have found successful? If so, please explain.

- o How did you come to these practices?
- o Are you aware of any "best practices" that other providers in the hospital have found successful? If so, please explain.

Appendix E: University of the Western Cape research ethics approval

UNIVERSITY of the WESTERN CAPE

OFFICE OF THE DIRECTOR: RESEARCH
RESEARCH AND INNOVATION DIVISION

Private Bag X17, Bellville 7535
South Africa
T: +27 21 959 2988/2948
F: +27 21 959 3170
E: research-ethics@uwc.ac.za
www.uwc.ac.za

25 April 2017

Dr R Coetzee
School of Pharmacy
Faculty of Natural Sciences

Ethics Reference Number: HS16/1/24

Project Title: Analysis of Clostridium difficile infection admissions and quality improvement interventions at public sector hospitals in Cape Town, South Africa

Approval Period: 03 March 2017 – 03 March 2018

I hereby certify that the Humanities and Social Science Research Ethics Committee of the University of the Western Cape approved the methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval. Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

PROVISIONAL REC NUMBER - 130416-049

Appendix F: National Health Laboratory Service study approval

Appendix F

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6142
Fax: +27 (0)11 386 6296
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

16 May 2016

Applicant: Dr Renier Coetzee
Institution: University of the Western Cape
Department: School of Pharmacy
Email: recoetzee@uwc.ac.za
Cell: 021 959 3665

Re: Approval to access National Health Laboratory Service (NHLS) Data

Your application to undertake a research project "**Analysis of *Clostridium Difficile* Infection Admissions and Quality Improvement Interventions at Public Sector Hospitals in Cape Town, South Africa**" using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required will be made available to you **without Patient Names** to conduct the proposed study as outlined in the submitted request.

Please note that the approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met.

- Ethics approval is obtained from a recognised SA Health Research Ethics Committee.
- Processes are discussed with the relevant NHLS departments (i.e. Information Management Unit and Operations Department) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- A final report of the research study and any published paper resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.
- NHLS Data cannot be used to track patients as no pre-approval/consent is obtained from Patients.

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research. Any data related queries may be directed to Sue Candy, Manager NHLS Corporate Data Warehouse, Tel: (011) 386 6036. Email: sue.candy@nhls.ac.za.

Yours sincerely,

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

Appendix G: UWC informed consent form

University of the Western Cape
Private Bag X17 Bellville 7535 South Africa Telegraph: UNIBELL Telex: 526661

Clinical Pharmacy and Pharmacology
Science Faculty, School of Pharmacy

Telephone: (27) (21) 959 3666
Fax: (27) (21) 959 1588

SUBJECT INFORMATION AND INFORMED CONSENT

UNIVERSITY OF THE WESTERN CAPE

Project Title: Analysis of Clostridium difficile infection admissions and quality improvement interventions at public sector hospitals in Cape Town, South Africa.

Investigator(s):

Principal Researcher: Dr. Renier Coetzee
School of Pharmacy
University of the Western Cape
Private Bag X17, Bellville 7535
South Africa

Tel: +27 (0)21 959 3665
Email: recoetzee@uwc.ac.za

Special Instructions:

This consent form may contain words that are new to you. If you read any words that are not clear to you, please ask the person who gave you this form to explain them to you.

Purpose:

You are being asked to take part in a research project analyzing *Clostridium difficile* infection.
You have been invited to participate because we would like to understand your perspective of this infection. The purpose of this research project is to learn how changes in hospital protocols affect infection rates, treatment, and understanding of the infection.

Procedures:

If you agree to take part in this research study, you will be asked a series of questions about *Clostridium difficile* infection in an interview format. The audio of this interview will be recorded. You will be asked about obstacles to treatment, resources available to patients, and aids for healthcare providers to identify and treat *Clostridium difficile*. You may also be asked to provide feedback on the use of a checklist for improving the treatment of Clostridium difficile infection. The session will last for 15-30 minutes.

Risks/Discomforts:

There is no anticipated discomfort for those contributing to this study, so risk to participants is minimal.

Benefits:

Although you may not directly benefit from taking part in this study, your participation in this project may help understand Clostridium difficile infection and improve treatment. Patients and healthcare providers may learn about possible resources.

Confidentiality:

Your identifying factors (name and/or employee type) will be kept private and will not be a part of the secure audio recording. The audio recording will be erased after the completion of this project.

Voluntary Participation/Withdrawal:

Your decision to take part in this research project is entirely voluntary. You may refuse to take part or you may withdraw from the project at any time without penalty.

Questions:

If you have any questions about the research now or during the study, please contact: Dr. Renier Coetzee, email: recoetzee@uwc.ac.za or Tel: +27 (0)21 959 3665

Statement of Your Consent:

I have read the above description of this research study interview. I have been informed of the risks and benefits involved, and all my questions have been answered to my satisfaction. I voluntarily agree to take part in this study. I understand that all efforts will be made to conceal my identity but that full confidentiality cannot be guaranteed. I understand I will receive a copy of this consent form. I hereby give consent for the information gathered from this interview to be used for education and training purposes, publication in journals, text books, or conference material. I understand that my consent or refusal will in no way affect my employment or health care.

_____

Printed Name of Participant

_____ _____

Participant's Signature Date

Statement of Consent to be audio recorded

I understand that audio recordings may be taken during the interview. I consent to having my audio recorded. I understand that audio recordings will be destroyed following project completion, and that no identifying information will be included in presentation of the results (publication in journals, text books, or conference material).

_____ _____

Participant's Signature Date

Ethical approval was granted by the University of the Western Cape on (Date) _____

Appendix H: *BMJ Global Health* publication

BMJ Global Health

Appendix H

Epidemiology and outcomes of *Clostridium difficile* infection among hospitalised patients: results of a multicentre retrospective study in South Africa

Laurel Legenza,[1] Susanne Barnett,[1] Warren Rose,[1] Monica Bianchini,[1] Nasia Safdar,[2] Renier Coetzee[3]

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[1]School of Pharmacy, University of Wisconsin-Madison, Madison, Wisconsin, USA
[2]School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin, USA
[3]School of Pharmacy, University of the Western Cape, Cape Town, South Africa

Correspondence to
Dr Renier Coetzee;
recoetzee@uwc.ac.za

ABSTRACT

Introduction Limited data exist on *Clostridium difficile* infection (CDI) in low-resource settings and settings with high prevalence of HIV. We aimed to determine baseline CDI patient characteristics and management and their contribution to mortality.

Methods We reviewed adult patients hospitalised with diarrhoea and a *C. difficile* test result in 2015 from four public district hospitals in the Western Cape, South Africa. The primary outcome measures were risk factors for mortality. Secondary outcomes were *C. difficile* risk factors (positive vs negative) and CDI treatment.

Results Charts of patients with diarrhoea tested for *C. difficile* (n=250; 112 *C. difficile* positive, 138 *C. difficile* negative) were reviewed. The study population included more women (65%). *C. difficile*-positive patients were older (46.5 vs 40.7 years, p<0.01). All-cause mortality was more common in the *C. difficile*-positive group (29% vs 8%, p<0.0001; HR 2.0, 95% CI 1.1 to 3.6). Tuberculosis (*C. difficile* positive 54% vs *C. difficile* negative 32%, p<0.001), 30-day prior antibiotic exposure (*C. difficile* positive 83% vs *C. difficile* negative 46%, p<0.001) and prior hospitalisation (*C. difficile* positive 55% vs *C. difficile* negative 22%, p<0.001) were also more common in the *C. difficile*-positive group. *C. difficile* positive test result (OR 4.7, 95% CI 2.0 to 11.2; p<0.001), male gender (OR 2.8, 95% CI 1.1 to 7.2; p=0.031) and tuberculosis (OR 2.3, 95% CI 1.0 to 5.0; p=0.038) were independently associated with mortality. Of patients starting treatment, metronidazole was the most common antimicrobial therapy initiated (70%, n=78); 32 *C. difficile*-positive (29%) patients were not treated.

Conclusion Patients testing positive for *C. difficile* are at high risk of mortality at public district hospitals in South Africa. Tuberculosis should be considered an additional risk factor for CDI in populations with high tuberculosis and HIV comorbidity. Interventions for CDI prevention and management are urgently needed.

Key questions

What is already known?

- Patients in South Africa have significant comorbidities distinct from high-resource countries, including a higher incidence of HIV and tuberculosis, which may uniquely increase patients' risk for *Clostridium difficile* infection (CDI).

What are the new findings?

- This study is the first examining risk factors, management, infection control and mortality among hospitalised patients in public hospitals in sub-Saharan Africa to our knowledge.
- The majority of patients treated for CDI received metronidazole, while the mortality of patients with a *C. difficile* positive result was significantly higher than similar patients testing negative with diarrhoea.
- In populations with high tuberculosis and HIV comorbidity, tuberculosis is an additional risk factor for CDI.

What do the new findings imply?

- Vancomycin should be considered as an alternative to metronidazole in populations with high prevalence of tuberculosis and immunocompromising conditions as a high mortality rate was observed in this study.

INTRODUCTION

Clostridium difficile infection (CDI) is an increasing global health concern resulting in severe diarrhoea, excessive healthcare costs, readmissions and mortality. Life-threatening complications resulting from CDI include sepsis, pseudomembranous colitis and toxic megacolon. The majority of CDI studies have been conducted in high-resource countries.[1] CDI incidence increased yearly in these settings after 2000 until recently; a decline in CDI incidence from 2011 to 2015 in long-term care settings was reported in association with decreased hospital fluoroquinolone use and detection of the NAP1/027 strain.[1 2] *C. difficile* remains the most common pathogen

implicated in hospital-acquired infections in the USA.[3 4] CDI in patients is associated with antibiotic use, which leads to disruption of normal flora and uninhibited growth of toxigenic *C. difficile*.[5] Antibiotics commonly associated with CDI include fluoroquinolones, third-generation cephalosporins, clindamycin and penicillins.[6] Advanced age is a noted risk factor for CDI, and commonly associated with CDI mortality in high-resource countries.[7] Additional risk factors for CDI include hospitalisation, inflammatory bowel disease, immunodeficiency, organ transplantation, chemotherapy, gastric acid suppression, chronic kidney disease and exposure to individuals with *C. difficile*.[6] The healthcare environment and patients in low-resource settings are distinct from high-resource settings. For example, South Africa has the lowest life expectancy in the world, 49.7 years, reducing the likelihood for elderly age to be a CDI risk factor.[8] Meanwhile, the relationship of CDI and the infectious diseases associated with mortality in this population is understudied. Thus, further investigation of CDI risk factors in these countries is urgently needed.

In South Africa, the leading causes of death are infectious diseases including tuberculosis, influenza/pneumonia and HIV, which may uniquely increase patients' risk for CDI.[9 10] South Africa has the largest known HIV epidemic in the world. Adult prevalence is estimated to be 18.9%, and 19% of people living with HIV globally reside in South Africa.[11] Tuberculosis incidence in South Africa is the sixth highest globally. Coinfection of tuberculosis in patients with HIV is a synergistic epidemic, including a disproportionate rate of HIV-associated tuberculosis deaths as 63% of tuberculosis cases are in patients with HIV.[12 13] Over the past decade, tuberculosis has surpassed HIV and cardiovascular disease as the leading cause of death.[14] While CDI studies in Africa are limited, two previous studies at a tertiary hospital in Cape Town, South Africa, documented 9%–22% of patients with diarrhoea tested *C. difficile* positive using different methods.[15 16] In one of these studies, patients with *C. difficile* positive results were associated with antibiotic use in the previous 28 days and hospitalisation within the previous 90 days compared with patients with negative results.[15] The prevalence of the NAP1/027 strain was 3.4%, which is substantially lower than in high-resource settings such as the USA, which has ranged from a 16.9% to 26.2% prevalence in recent studies.[15 17]

Understanding the epidemiology of CDI in low-resource settings is essential to improve identification, prevention and treatment measures. In the present study, we identify patient CDI characteristics and management in resource-limited public district level hospitals and their contribution to mortality.

METHODS

Local infectious disease leaders were consulted early in study design, starting in August 2015. These leaders identified CDI as a critical public health challenge in South Africa because of its increasing incidence and high morbidity and mortality globally, lack of local studies and vulnerable populations with HIV and tuberculosis locally. In addition to the lack of CDI studies performed in these hospitals and this patient population, focus on district hospitals was also recommended due to the scarcity of CDI data at this level. Subsequently the University of the Western Cape Research Ethics Committee, National Health Laboratory Service (NHLS) and Western Cape Department of Health granted approval for the first CDI epidemiological study in South African district level hospitals.

On approval, a multicentre, retrospective chart review was conducted at four district-level hospitals, averaging 265 inpatient beds, in Cape Town, South Africa. The study included hospitalised adult patients (>18 years of age) with diarrhoea and either a positive or negative *C. difficile* PCR test result from one or more stool samples during the year 2015. These patients were identified from a list of *C. difficile* test results provided by NHLS, which is a national network of diagnostic laboratories that serve 80% of the South African population, including the Western Cape Department of Health hospitals. All stool samples from the district-level hospitals included in this study were sent to the NHLS laboratory at the nearest tertiary-level hospital. Standardised NHLS protocols indicated PCR testing for all eligible samples in 2015 (NHLS does not perform *C. difficile* tests on solid stool samples or patients with a recent *C. difficile* positive result). All patients included in the study had diarrhoea that took the shape of the container and clinical suspicion for CDI. A minimum number of stools within 24 hours was not required for study inclusion as frequency was inconsistently documented. Any additional aetiologies tested were not included in the laboratory report. Test results originating from paediatric patients, outpatient clinics or day surgery patients were excluded. Patients with tests ordered in the emergency department were included if the patient was subsequently admitted to the hospital.

The primary outcome of this study was the identification of risk factors for mortality in South African patients in the Western Cape with diarrhoea. Secondary outcomes were risk factors for a *C. difficile* positive result compared with a *C. difficile* negative result, and within this group, risk factors for mortality and management of CDI.

The 2015 medical records for any patient with a *C. difficile* test result were reviewed from August 2016 to April 2017. Data collection was subject to the available processes for medical record review and availability of files at each individual hospital. Paper folders were requested from the medical records department at each hospital and reviewed by study personnel onsite. At one hospital, medical records were accessible electronically by access granted to view scanned files of the patient folders remotely. The review included all available patient records with a positive *C. difficile* test result. At each hospital, an equal number of *C. difficile*-positive and negative patient charts were requested and reviewed

if available. At most hospitals, the number of negative test results was much larger than positive results. Therefore, all identified patients with a positive *C. difficile* test result were requested, while patients with a negative test result were randomly selected following an autogenerated random number process. The randomisation of the negative chart numbers was performed to address selection bias. If the total number of patients tested at each hospital was less than 25, all available charts were reviewed. As this is the first epidemiologic study in district-level hospitals, the magnitude of tests was difficult to predict. In this study design, the number of positive results limited sample size during the year evaluated and an a priori sample size calculation was not performed.

Use of a structured data collection tool allowed for review of all clinical and laboratory notes available in the medical record from the hospital admission including the *C. difficile* test. Pertinent records prior to the admission were also reviewed using the same tool to determine medical history and previous antibiotic exposure, and postadmission records were reviewed to determine patient outcomes, recurrence and mortality. Data collected included demographics (gender, age, allergies), comorbid conditions (HIV, tuberculosis, multidrug-resistant tuberculosis, diabetes, cardiovascular conditions: heart failure, hypertension, hyperlipidaemia, other cardiovascular conditions, malignancy, inflammatory bowel diseases: ulcerative colitis, Crohn's, other immunocompromising condition), hospitalisations prior to the current admission (0–30 and 31–90 days prior to test order) and previous antibiotic exposure, including a single dose (penicillins, quinolones, carbapenems, cephalosporin, clindamycin or other), and indication in prior 30 and 90 days from date of written CDI order, CDI history (current episode is documented as first CDI episode, recurrence, unknown if first episode or recurrence), clinical presentation (diarrhoea, temperature (>38°C), haematochezia, pseudomembranous colitis), dates of admission, rehydration, loperamide use, CDI antibiotic treatment, CDI-related infection control (isolation and contact precautions) and reason for hospitalisation.

Data were analysed using Stata SE statistical software (V.15.0, StataCorp, College Station, Texas, USA). Summary statistics for infection management were determined, including antibiotic treatment and infection prevention and control components. Length of stay (LOS) was summarised and compared by t-tests both by *C. difficile* test result and hospital mortality to express mean, median and statistically significant differences. Univariate summary statistics were calculated for age and gender of individual patients. X^2 tests were conducted by *C. difficile* test result and mortality for patient characteristics and CDI risk factors. A survival analysis with the Gehan-Breslow-Wilcoxon test was determined for patients with *C. difficile* positive PCR versus *C. difficile* negative PCR in GraphPad Prism (V.6, GraphPad Software, La Jolla, California, USA), with a start date equal to when an order for *C. difficile* test was written and end date the day of mortality or discharge. Censoring occurred for patients discharged before 30 days to account for uncertainty of survival and readmission after discharge. Patients with a clinic visit or hospital admission occurring greater than 30 days after the *C. difficile* test were categorised as survivors. P values ≤0.05 were considered significant. All variables identified as at least marginally significant (p<0.10) predictors in the univariate mortality analysis were included in the model. Independent predictors of all-cause mortality were determined via a separate multivariable logistic regression.

RESULTS

Overall, 652 *C. difficile* PCR tests were conducted in 2015 from the four hospitals included; 19 of these had an error result and were excluded. Forty-one of the 291 patient charts requested were excluded because either the patient chart was unavailable or missing, the chart lacked adequate documentation to review related to the test date, or the test met exclusion criteria for not occurring during a hospitalisation (eg, outpatient clinic, day surgery). Of 139 positive results, 112 results and corresponding charts were reviewed and of 494 negative results, 138 negative results were reviewed (total n=250; figure 1). Two tests were reviewed for one patient during a 76-day LOS. All other test results reviewed were from unique hospitalisations. The 250 test results reviewed represent 225 individual patients.

Patient characteristics analysed by test result in the univariate analyses are presented in table 1. Significant differences were found in the patient demographics in patients testing positive versus negative for *C. difficile* including age, tuberculosis, prior hospitalisation and specific antibiotic use. Mean age and gender distribution was calculated for 225 individual patients (102 *C. difficile*+; 123 *C. difficile*–), excluding subsequent test results from patients with more than one test in the study period. The mean age for the *C. difficile*-positive patients was 46.5 years compared with 40.7 years for *C. difficile*-negative patients (p<0.01). There were more women in the study population (65%). However, mean age was similar between men and women in this study overall (43.4 vs 43.3 years, respectively).

Presence of comorbid infectious diseases also proved to be a significant variable, particularly with regard to tuberculosis. More patients testing positive for *C. difficile* also had tuberculosis (*C. difficile* positive 54% vs *C. difficile* negative 32%, p<0.001). HIV rates were high in both *C. difficile*-positive and *C. difficile*-negative patients (71% vs 80%, respectively; p=0.07). Of HIV-positive patients with a *C. difficile* test result, the majority had CD4 counts consistent with AIDS (CD4 <0.2 x10^9 cells/L ; *C. difficile* positive 81%; *C. difficile* negative 81%; n=178).

Analysis of *C. difficile* test results confirmed prior hospitalisation and antibiotic exposure are important CDI risk factors among patients included in the study. Recent prior hospitalisation was more common in *C. difficile*-positive

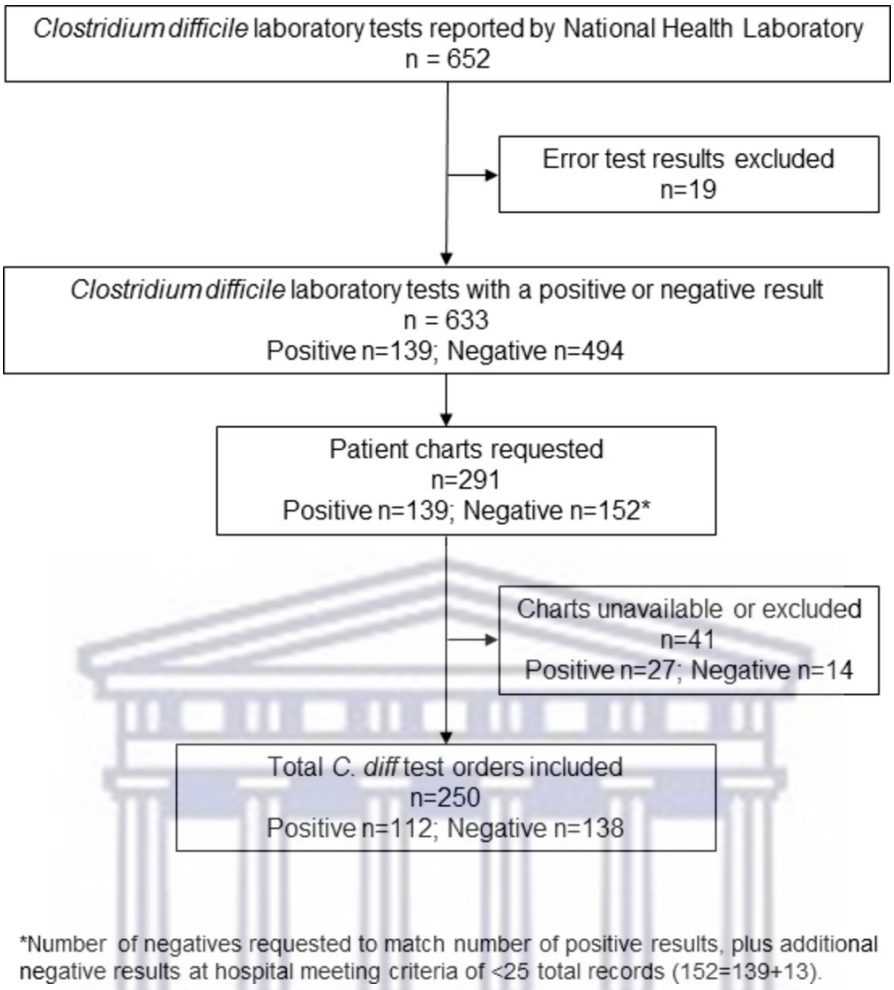

Figure 1 Patient *Clostridium difficile* test result inclusion.

patients for both hospitalisation 30 and 90 days prior to the admission (p<0.001). Thirty-day prior antibiotic exposure to all antibiotic classes reviewed was significantly higher in the *C. difficile*-positive group (table 1). The most common antibiotic class with recent prior exposure to patients tested for *C. difficile* was cephalosporins, with half of *C. difficile*-positive patients receiving a cephalosporin in the 30 days prior to the *C. difficile* test order (vs 34% in *C. difficile* negative, p<0.02). Documentation of tuberculosis antibiotic treatment prior to admission was insufficient to report as prior tuberculosis treatment was not consistently detailed for patients with treatment ordered in hospital. Prescriptions outside the hospital and onsite clinic were not captured if not noted in the admission clinical notes.

Mortality in patients with diarrhoea was more common in the *C. difficile*-positive group (29% vs 8%, p<0.0001). A Kaplan-Meier survival analysis (p=0.0087) for patients evaluated following a *C. difficile* test order (figure 2) found an all-cause mortality HR of 2.0 (95% CI 1.1 to 3.6) in patients with a *C. difficile* positive test. All mortality identified occurred in-hospital.

Variables with marginal associations (p<0.01) with mortality are presented in table 2. A logistic regression including these variables, 30-day mortality, *C. difficile* test result, prior hospitalisation (30 and 90 days), critical care admission, tuberculosis, sex, multidrug-resistant tuberculosis and haematochezia was performed (table 3) for mortality as a dependent variable. HIV, immunosuppression and malignancy did not meet criteria for inclusion in the model. Multidrug-resistant tuberculosis perfectly predicted mortality, so the variable was dropped from the model (n=12). An independent risk of mortality in patients with diarrhoea with a *C. difficile* positive test result versus *C. difficile* negative test (OR 4.7, 95% CI 2.0 to 11.2; p<0.001) was found. Clinically meaningful independent variables associated with mortality also included comorbid tuberculosis (OR 2.3, 95% CI 1.0 to 5.0; p=0.038) and male sex (OR 2.8, 95% CI 1.1 to 7.2; p=0.031). Prior antibiotic exposure overall or with any specific antibiotic class and hospitalisation were not independently associated with mortality.

Components of *C. difficile* management for the *C. difficile*-positive patients were assessed (n=112). Intravenous rehydration was widely provided (95%) but oral rehydration was rarely documented (12%). Contact precautions were documented for 36% of patients. Of the 21% of patients with a *C. difficile* positive result who were allocated to an isolation room, 16 of these 24 patients (67%) were also diagnosed with comorbid tuberculosis.

Table 1 Patient characteristics

	Clostridium difficile laboratory test result (PCR)		
	Positive (n=112)	Negative (n=138)	P values
Patient characteristic			
Age average (years)*	47	40	<0.01
Sex (female)*	68%	63%	0.43
Documented HIV	71%	80%	0.07
CD4 0.2 x10^9 cells/L †	81%	81%	0.96
Documented tuberculosis	54%	32%	<0.001
Multidrug-resistant tuberculosis	9%	3%	0.04
Prior exposure to each *C. difficile* test			
Hospitalised 30 days prior to admission	52%	22%	<0.001
Hospitalised 31–90 days prior to admission	44%	23%	0.001
30-day antibiotic exposure	83%	46%	<0.001
Penicillin	21%	11%	0.02
Quinolone	25%	10%	<0.01
Carbapenem	22%	4%	<0.001
Cephalosporin	50%	34%	<0.01
Clindamycin	4%	0%	0.03
31–90 days of antibiotic exposure	29%	5%	<0.001
Penicillin	12%	1%	0.001
Quinolone	8%	1%	0.01
Carbapenem	2%	0%	0.12
Cephalosporin	13%	3%	<0.01
Clindamycin	0%	0%	

*Mean age and gender distribution calculated for 225 individual patients, excluding patients with more than one test (102 *C. difficile*+; 123 *C. difficile*–).
†Of HIV+ patients, patient CD4 counts were available for 178 *C. difficile* test results (74 *C. difficile*+; 104 *C. difficile*–).

Loperamide, contraindicated in CDI, was administered to 44% of all patients reviewed, which includes 41% of *C. difficile*-positive and 46% of *C. difficile*-negative patients. Loperamide was discontinued after documentation of a *C. difficile* positive result in 22% of these patients.

Twenty-nine percent of *C. difficile*-positive patients did not have documented treatment. Explanations observed for lack of treatment included patient improvement (n=2, 15%), no follow-up or documentation of *C. difficile* test result during admission while the result was finalised on a date the patient was still hospitalised (n=8, 25%), patient discharge or transfer before test result finalised (n=13, 41%) and mortality before result finalised (n=6, 19%). Metronidazole was the most common antimicrobial

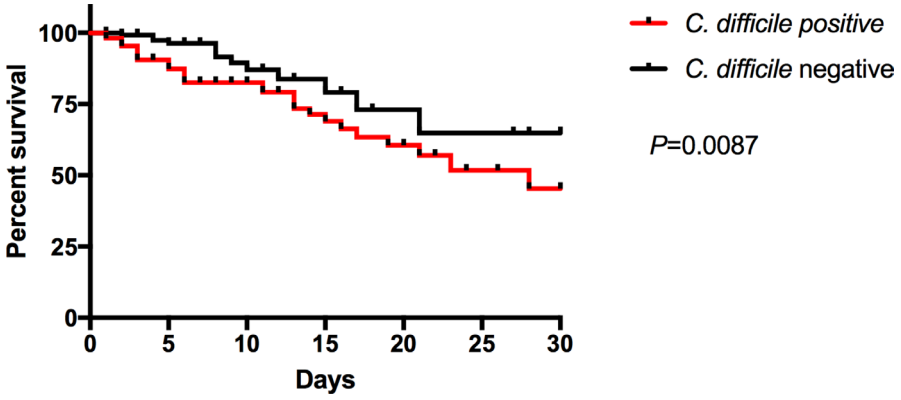

Figure 2 Survival curve for hospitalised patients with diarrhoea following a *Clostridium difficile* test. HR 2.0 (95% CI 1.1 to 3.6).

Table 2 Univariate analysis of risk factors for mortality found to be marginally significant (p<0.1)

Variables	P values
Clostridium difficile test result	0.000
Hospitalised 30 days prior to admission	0.004
Critical care admission	0.014
Tuberculosis	0.046
Gender	0.051
Multidrug-resistant tuberculosis	0.085
Hospitalised 90 days prior to admission	0.094
Haematochezia	0.097

therapy initiated (70%, n=78). Metronidazole strength was most often 400 mg (95%) for initial treatment and usually ordered every 8 hours (97%), consistent with the South African Standard Treatment Guidelines.[18] Treatment durations, however, varied from the 10-day guideline recommendation. Duration of initial metronidazole therapy ordered ranged from 5 to 14 days, with 10 days being the most commonly prescribed (45%). Metronidazole orders less than or equal to 7 days were written for 30% of patients. *C. difficile* antibiotic treatment prescribing rates were not significantly different across the four hospitals.

Two patients were treated with oral vancomycin monotherapy for initial treatment. Vancomycin was added to or replaced metronidazole treatment in 14.3% of patients (n=16). When oral vancomycin was added, the frequency of administration was consistent with every 6 hours as per South African Standard Treatment Guidelines for CDI in 47% of orders.[18] The most common duration of vancomycin was 10 days (44%) and ranged from 5 to 15 days (31% <7 days). All initial CDI treatment was ordered for oral administration. Intravenous vancomycin was added to metronidazole in two patients (dose 600 and 1000 mg once daily), but we were unable to document whether this vancomycin administration might have been for CDI management or another infection. One patient was changed from oral to intravenous metronidazole for three doses, then changed back to oral administration.

Overall, mean LOS for all hospitalisations reviewed was 10.2±11.0 days (median 7 days, range 0–76 days). Mean LOS for *C. difficile*-positive patients discharged from the hospital was significantly longer (11.3±10.5 days, median 9 days) compared with *C. difficile*-negative patients (8.2±8.5 days, median=6.5 days, p=0.02). Recurrence could not be accurately assessed on all patients due to inconsistent records before and after the admission evaluated.

DISCUSSION

Although there is a wealth of data on CDI epidemiology and outcomes from high-resource countries, research from low-resource countries is sparse. This analysis and these data are the first examining CDI, risk factors, management and mortality among hospitalised patients in South Africa at district-level hospitals to our knowledge. Understanding how CDI is currently being treated and which patients are at greatest risk in South Africa is the first step to designing and implementing quality improvement interventions. Prevalence of tuberculosis appears to be strongly associated with CDI incidence and to interact with demographic and other risk factors influencing positive *C. difficile* results and mortality. Significantly more patients in our study who tested positive for *C. difficile* had tuberculosis (p<0.001). *C. difficile* positive test result, tuberculosis and male sex were found to be independent risk factors for 30-day mortality in this study. Consistent with known CDI risk factors in high-resource settings, prior hospitalisation and antibiotic exposure were strongly associated with a positive *C. difficile* test result. Tuberculosis should be considered a risk factor for CDI in this population, as associations and mortality outcomes in this study are revelatory. Tuberculosis is a less critical risk factor in high-resource settings where prevalence is low. Targeted CDI interventions may improve the high mortality identified and apply to similar low-resource settings in the future.

A post hoc power analysis of *C. difficile* result and mortality for our sample size, 112 *C. difficile* positive results and 138 *C. difficile* negative results was performed. The calculated effect size of 0.27 indicated we had 99% power to detect this difference. However, it may be

Table 3 Logistic regression analysis of 30-day mortality

Variable	OR	SE	P values	95% CI
Clostridium difficile test result	4.7	2.1	0.000	2.0 to 11.2
Hospitalised 30 days prior to admission	0.97	0.42	0.952	0.42 to 2.3
Hospitalised 90 days prior to admission	1.2	0.51	0.676	0.51 to 2.7
Critical care admission	13.8	17.9	0.044	1.0 to 176
Tuberculosis	2.3	0.91	0.038	1.0 to 5.0
Gender	2.8	1.3	0.031	1.1 to 7.2
Multidrug-resistant tuberculosis	1	–	–	–
Haematochezia	0.14	0.15	0.069	0.02 to 1.2

difficult to extrapolate these findings to patients treated in the private sector in South Africa, where HIV and tuberculosis prevalence is significantly lower. A weakness of this study includes the limitations of the retrospective design and data. The chart review included primarily handwritten clinical notes that occasionally required interpretation; assistance from local collaborators and study team members was essential in the data collection phase. The data collection was also limited to only information included in the patient charts. For example, prior antibiotics and hospitalisations at institutions other than a patient's local hospital would be missing, as would any paper records not properly combined or available during data collection. Furthermore, information bias from any missing data regarding severe infections or severe comorbidities such as cancer could affect the results. The study data are insufficient to delineate if the association of CDI and tuberculosis is due to disease pathogenesis or antibiotics administered for tuberculosis. Patients were unable to be evaluated for severe disease as defined by CDI consensus guidelines as laboratory data were often limited in this retrospective review. It is possible, however, that many patients in this study may have had severe CDI as evidenced by the high mortality rate of *C. difficile*-positive patients, independent of other variables. Despite the limitations of this study, we are reporting novel, needed and independently associated factors of significance.

The results of this study indicate key differences relating to CDI risk factors and mortality between high and low-resource countries, specifically regarding associations of CDI to tuberculosis, sex, age and antibiotic exposure. First, tuberculosis is not commonly included in a list of risk factors for CDI, as this infection is relatively infrequent in high-resource countries where CDI has been most studied. The associations of tuberculosis and CDI could be related to prior healthcare exposure and the use of second-line tuberculosis antibiotics, including fluoroquinolones. A study conducted at tertiary hospitals in South Korea found an increased risk of mortality in patients with concomitant CDI and tuberculosis, compared with CDI alone.[19] This suggests there may be a pathophysiologic or antibiotic-induced relationship between CDI and mortality in patients with tuberculosis. Second, data on sex/gender differences in CDI-associated mortality are limited. Two previous studies implicate male sex with CDI and complications. The first is a study limited to a single centre in France identifying male sex as a predictor of severe CDI. Another is a study that reported male patients with proton pump inhibitor use have a higher risk of CDI mortality.[20 21] Tuberculosis incidence is higher in men in South Africa (male 226 000 vs female 154 000) and a tendency for men to present for healthcare later in their disease course has been reported in South Africa and globally.[22 23] Despite the propensity for CDI-related mortality in men, previous studies in high-resource settings report women are more likely to have CDI.[7 24] Therefore, distinct CDI-associated risks may exist between men and women. Third, tuberculosis infection may also be a factor in the age of patients hospitalised with CDI in low-resource settings. The relatively young average age of patients included in this study likely reflects the population burden of high tuberculosis incidence in South Africa in the age range of 25–44 years.[22] Finally, the antibiotic exposure observed in this study resembles patterns observed in England prior to implementing prescribing patterns to control CDI, an element of antimicrobial stewardship.[25] In addition to continued strengthening of antimicrobial stewardship efforts in South Africa, significant differences discussed in this manuscript highlight the need for population-tailored CDI guidelines, including identification of population-specific CDI risk factors and interventions.

Using the results of this study, clinicians and policymakers in areas with a high prevalence of tuberculosis and HIV should carefully evaluate which patients are at highest risk for a poor outcome from CDI and ensure appropriate initial treatment. The high mortality associated with CDI in this study also highlights the need for prompt identification, appropriate treatment, and infection prevention and control measures in populations with high HIV and tuberculosis prevalence. The 2010 CDI Infectious Diseases Society of America guidelines recommended first-line therapy with oral metronidazole for mild to moderate disease. Since publication of these guidelines, further studies have supported the use of vancomycin as a first-line therapy. Subsequently, the 2017 guidelines now restrict metronidazole to initial non-severe CDI, when other therapies are contraindicated or unavailable.[26] The majority of patients treated for CDI in this study received metronidazole, and were switched to vancomycin only if initial therapy with metronidazole was proven ineffective. The high mortality rate of patients with CDI in our study suggests that South African patients may benefit from first-line vancomycin therapy as this medication has been shown to have higher clinical cure rates and significantly lower risk of mortality in severe CDI.[27 28] If oral vancomycin therapy is not adopted as first-line, CDI antibiotic treatment decisions should include markers beyond white cell count, especially for immunocompromised patients and in settings where laboratory results are limited. Risk classifications for severe CDI per the European Society of Clinical Microbiology and Infectious Diseases include older age (>65), serious comorbidity, immunodeficiency and intensive care unit admission.[29]

CONCLUSIONS

This study provides valuable information to healthcare providers, hospital administrators and policymakers regarding the demographics of hospitalised patients with CDI and CDI-associated patient mortality. Tuberculosis comorbidity should be considered a risk factor for CDI in addition to antibiotic use and prior healthcare exposure in populations with high tuberculosis and HIV comorbidity. Patients testing positive for *C. difficile* have

a significantly higher and independent risk of mortality compared with patients with diarrhoea testing negative at public district hospitals in South Africa. These results can be used to identify patients at risk of developing CDI and to improve the quality of care provided to patients with CDI in similar settings. Our results indicate improved CDI prevention, assessment and management is urgently needed in the Western Cape province.

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Contributors LL designed the study, designed data collection, monitored data collection for the whole study, collected data, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. She is the guarantor of the study. SB, WR and NS provided guidance on the study and revised the paper. MB designed data collection tools, collected data and revised the paper. RC facilitated the collaborative project between the University of the Western Cape and the University of Wisconsin, provided guidance on the study and revised the paper.

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Disclaimer The lead author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Competing interests None declared.

Patient consent The Ethics Committee did not require consent for this retrospective study and quality improvement project.

Ethics approval The study was approved by the University of the Western Cape Department of Research Development, Ethics Reference No HS/16/1/24.

Provenance and peer review Not commissioned; externally peer reviewed.

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- Analysis
- Practice
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Appendix J: ***Antimicrobial Resistance & Infection Control*** **publication**

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Appendix J

Antimicrobial Resistance and Infection Control

RESEARCH Open Access

Clostridium difficile infection perceptions and practices: a multicenter qualitative study in South Africa

Laurel Legenza[1,2*], Susanne Barnett[1], Warren Rose[1], Nasia Safdar[3], Theresa Emmerling[1], Keng Hee Peh[1] and Renier Coetzee[2]

Abstract

Background: *Clostridium difficile* infection (CDI) is understudied in limited resource settings. In addition, provider awareness of CDI as a prevalent threat is unknown. An assessment of current facilitators and barriers to CDI identification, management, and prevention is needed in limited resource settings to design and evaluate quality improvement strategies to effectively minimize the risk of CDI.

Methods: Our study aimed to identify CDI perceptions and practices among healthcare providers in South African secondary hospitals to identify facilitators and barriers to providing quality CDI care. Qualitative interviews (11 physicians, 11 nurses, 4 pharmacists,) and two focus groups (7 nurses, 3 pharmacists) were conducted at three district level hospitals in the Cape Town Metropole. Semi-structured interviews elicited provider perceived facilitators, barriers, and opportunities to improve clinical workflow from patient presentation through CDI (1) Identification, (2) Diagnosis, (3) Treatment, and (4) Prevention. In addition, a summary provider CDI knowledge score was calculated for each interviewee for seven components of CDI and management.

Results: Major barriers identified were knowledge gaps in characteristics of *C. difficile* identification, diagnosis, treatment, and prevention. The median overall CDI knowledge score (scale 0–7) from individual interviews was 3 [interquartile range 0.25, 4.75]. Delays in *C. difficile* testing workflow were identified. Participants perceived supplies for CDI management and prevention were usually available; however, hand hygiene and use of contact precautions was inconsistent.

Conclusions: Our analysis provides a detailed description of the facilitators and barriers to CDI workflow and can be utilized to design quality improvement interventions among limited resource settings.

Keywords: Healthcare associated infection, Infection control, Qualitative study, Antimicrobial stewardship, Global health

Background

Clostridium difficile infection (CDI) is an increasingly important healthcare-associated infection associated with long hospitalisations and high patient morbidity and mortality [1]. CDI often results from normal gut bacterial disruption due to broad-spectrum antimicrobial use, allowing for overgrowth of toxigenic *C. difficile*. CDI outbreaks have been reported extensively in the United States (US) and Europe over the last two decades. CDI in these hospitals is prevalent supporting extensive CDI prevention and control measures. However, CDI is understudied in low and limited resource settings, including nearly all African countries. Where limited data exists, a study at a tertiary hospital in Cape Town, South Africa found 22% of stool samples from patients with suspected CDI diarrhoea were *C. difficile* positive [2]. In addition, patients in South Africa are disproportionately affected by HIV and tuberculosis (TB) and therefore also experience known CDI risk factors of prior hospital and antibiotic exposure—exposures that

* Correspondence: Legenza@wisc.edu
[1]University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, WI 53705, USA
[2]University of the Western Cape School of Pharmacy, Robert Sobukwe, Cape Town 7535, South Africa
Full list of author information is available at the end of the article

can uniquely contribute to an increased risk of CDI and poor outcomes [3, 4].

Treatment of CDI requires a comprehensive approach that includes infection prevention and control (IPC) measures to limit transmission and prevent outbreaks. Although no CDI IPC guidelines exist specific to African countries, the Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases guidelines consistently recommend IPC components of antimicrobial stewardship programs (ASP) which include effective environment cleaning, patient isolation, use of personal protective equipment such as gowns and gloves, surveillance, and education [5]. These evidence-based recommendations are key to effective CDI management. The feasibility of using these recommendations in populations with limited healthcare resources has not been established. In addition, healthcare provider knowledge of CDI and the guidance to effectively mitigate and manage patient populations at higher risk for CDI is unknown.

Provider knowledge of CDI and treatment measures are essential to both successfully manage CDI and prevent disease transmission. An assessment of current facilitators and barriers to CDI identification, management, and prevention is needed to design and evaluate improvement strategies to effectively minimize the risk of CDI. To our knowledge, no comprehensive study of barriers and facilitators to CDI workflow (identification, diagnosis, treatment, and prevention) in Sub-Saharan Africa exists. Our study aims to fill this gap by eliciting CDI perceptions and management practices among healthcare providers in South African secondary hospitals to uncover facilitators and barriers to providing quality CDI care.

Methods

Data collection

We utilized a qualitative approach to elicit health care providers' perceptions of barriers and facilitators to CDI management because it provides detailed process oriented results. We conducted semi-structured interviews and focus groups among clinical providers at three secondary hospitals in South Africa. A Systems Engineering Initiative for Patient Safety (SEIPS) model served as a framework for the interview guide. The SEIPS framework connects work systems to patient and organizational outcomes, while including interactions in the work system between available tools, people, tasks, the internal environment, and the organization [6]. The semi-structured interview assessed each subject's CDI knowledge and traced workflow from patient presentation with CDI symptoms through CDI 1.) Identification, 2.) Diagnosis, 3.) Treatment, and 4.) Prevention. Interview questions were structured to reveal facilitators and barriers to these CDI workflow steps and opportunities to improve CDI treatment. The interview guide included optional probes to use when appropriate to gather additional information. When participants revealed a lack of CDI knowledge from the preliminary questions, the interview was then modified to contain general questions about diarrhoea management. As a qualitative study, the interviewer could use information gathered from prior interviews to direct future interview discussions and build on emerging concepts. For example, asking for further detail and implications on processes mentioned with open-ended questions.

Participants

Providers working in three public secondary (district) level hospitals in the Western Cape, Cape Town Metropole, South Africa were invited to participate in this study. The three participating hospitals, averaging 265 inpatient beds overall, were previously selected to be included in a CDI quality improvement intervention. Our study aimed to interview, at minimum, 15 providers among five provider types including front-line nurses, nurse managers, pharmacists, junior physicians (registrars and medical officers), and senior physicians (consultants and department administrators). Semi-structured interviews and focus groups occurred August–November 2016.

Study investigators included healthcare providers from the US and South Africa with local hospital affiliations. The interviewers, a study investigator and a visiting US pharmacy resident, recruited front-line healthcare providers with convenience and snowball sampling, and recruited senior providers with purposive sampling. There were no participant exclusion criteria. Interviews were conducted as focus group discussions if preferred by participants. Participants were provided an informed consent document approved by the ethics committee prior to the interview and could decline participation at any time. Interviews were conducted by the interviewer in consultation rooms and offices. All interviews were conducted in English by one of the two interviewers with questions from a semi-structured interview guide and probing techniques by the interviewer. Interviews continued until thematic saturation was observed regarding barriers and facilitators for CDI treatment and management. The University of the Western Cape Research Ethics Committee granted approval for this qualitative study.

Data analysis

Interview audio recordings were transcribed verbatim and checked for accuracy. Data analysis included coding

to factors determined a priori (including key workflow steps: 1) Identification, 2) Diagnosis, 3) Treatment, and 4) Prevention) as well as inductive coding to emerging themes [7]. Two individuals from a team of three coders (LL, TE, and KP) conducted each coding phase. Paired coding with two coders per phase was performed to minimize bias. Coding schema was created to reconcile local medical terminology. Discrepancies in coding were resolved by consensus. Kappa scores were calculated to assess coding agreement at a mid-point and at the conclusion of coding. While we had initially planned to map results with the SEIPS framework, CDI management knowledge was significantly lower than expected and insufficient to frame the results in terms of tools, people, tasks, the internal environment, and the organization. Alternatively, we mapped coded themes to the workflow structure identified from the interviews.

After identifying large discrepancies in health care provider knowledge regarding CDI during the interview process, a scoring system was developed to categorize participants' CDI knowledge from their interview responses (Table 1). The intent of the assessment was to quantify the unexpected differences. With the knowledge assessment, one knowledge point was possible from each of the following seven CDI-related components: signs and symptoms (e.g. diarrhoea), characteristics of bacteria (e.g. microbiology, virulence mechanism, disruption of normal flora, opportunistic), hand hygiene (e.g. soap and water needed to clean hands, not just alcohol), treatment (e.g. metronidazole, oral vancomycin, fecal transplant, contraindication with loperamide), contact precautions/isolation (contagious), risk factors (e.g. healthcare exposure, antibiotic use, immunocompromised by medication or illness [cancer, HIV status, CD4 count < 200] proton pump inhibitor use), and diagnosis (e.g. stool sample and testing methods, polymerase chain reaction[PCR]/toxin detection). The following responses did not receive a point allocation: 1) only stating 'bacterial infection' for characteristics of bacteria, 2) stating a non-specific sign and symptoms of infection or illness without stating diarrhoea, 3) stating rehydration (electrolytes) without specific antibiotic treatment name. Total knowledge score from each individual interview was further classified into four categories: 'no knowledge' (0–1 point), 'limited knowledge' (2–3 points), 'moderate knowledge' (4–5 points), and 'advanced knowledge' (6–7 points). Each CDI knowledge category was also scored across all interviewees. Researchers conducted subgroup analysis of knowledge level based on occupation and performed analysis of individual CDI assessment knowledge categories by participant and occupation. The two focus group interviews were excluded from the knowledge assessment analysis due to potential knowledge score overestimation. However, dialogue from the group interviews was included in the qualitative analysis. All analyses were conducted using NVIVO software (Version 11, QSR International).

Table 1 *Clostridium difficile* knowledge assessment

Criteria for *Clostridium difficile* knowledge	Points
Signs and symptoms (diarrhoea)	1
States characteristics of bacteria (any mention of: microbiology, virulence mechanism, disruption of normal flora, opportunistic)	1
Soap and water needed to clean hands, not just alcohol	1
Treatment options (any mention of: metronidazole, oral vancomycin, fecal transplant, contraindication with loperamide)	1
Contact isolation needed (or contagious)	1
Risk factors (immunocompromised, antibiotic use, proton pump inhibitors)	1
Diagnosis (stool sample, testing methods [PCR/toxins])	1
Total points	=
No knowledge = 0–1[a] Limited knowledge = 2–3 Moderate knowledge = 4–5 Advanced knowledge = 6–7	

[a]Point allocation of 1 is considered no knowledge because there are multiple diseases associated with any one of the criteria, unless person states characteristics of bacteria

Results

A total of 26 semi-structured interviews were conducted with healthcare providers (11 nurses, 4 pharmacists, 11 physicians) of various rankings (Table 2). In addition, two focus groups were conducted; one with seven nurses and the second with three pharmacists, resulting in 36 study participants (Table 2). Kappa scores indicated high intercoder agreement (midpoint kappa = 0.71, final kappa 0.63). The median overall CDI knowledge score from the 26 individual interviews was 3 [interquartile range 0.25, 4.75]. Subgroup median knowledge scores and an analysis of responders' knowledge of each category are presented in Table 3. Inductive themes were coded for processes required for CDI workflow and organizational culture (beliefs and attitudes) regarding change (i.e. the ease of positive change at the organization or 'change culture') in order to inform future interventions. Healthcare provider responsibility and accountability for components of CDI management emerged as an organizational culture theme from the interviews. Thematic saturation of barriers and facilitators to CDI management was reached across the health care provider types (i.e. no additional themes emerged after iterative analysis of 26 interview and two focus group transcripts) [8]. CDI workflow steps are presented along with corresponding knowledge scores, barriers, and facilitators, (Section I: Workflow) and followed by organizational culture themes (Section II: Organizational Culture).

Table 2 Occupations and stated titles of healthcare providers interviewed

Healthcare Provider Occupation	Participants	Interviews
Nurse		
Operational managers or Assistant manager	4	4
Registered nurse or unspecified nurse	4	4
Infection Prevention and Control Nurse	2	2
Nurse Training Clinical Program Coordinator	1	1
Ward Nurses Focus Group Interview	7	1
Subtotal:	18	12
Pharmacist		
Pharmacist	4	4
Pharmacist Focus Group Interview	3	1
Subtotal:	7	5
Physician		
Head of Department	2	2
Consultant	1	1
Unspecified physician	1	1
Registrar	1	1
Medical officer	5	5
Intern	1	1
Subtotal:	11	11
Total (N)	36	28

Section I: Workflow

Figure 1 presents workflow depicted from interview results, along with facilitators and barriers to CDI management summarized in the context of the CDI workflow, including the previously identified steps of CDI identification, diagnosis, treatment, and prevention. When CDI is suspected, a stool sample is sent to an offsite laboratory for *C. difficile* identification by PCR. Following CDI diagnosis, treatment and infection prevention and control measures are initiated. Processes were consistent between healthcare providers with knowledge of the workflow step.

Identification and healthcare provider knowledge

CDI identification requires knowledge of the bacteria, risk factors and clinical suspicion when patients present with CDI signs and symptoms. A major barrier to identification is low CDI knowledge. Ten interviews (6 nurses, 4 pharmacists) scored as 'no CDI knowledge' (Table 3). One participant candidly revealed the lack of CDI knowledge.

> *"It's actually the first time that I hear about it, to be honest"* - Pharmacist

CDI signs and symptoms were most commonly known by healthcare providers ($n = 16$, 61.5%). Thirteen (50%) participants could not describe CDI risk factors that could prompt clinical inquiry for CDI; this knowledge gap creates a potential barrier for prompt identification. Two physicians reported extensive experience with CDI in the United Kingdom. A recurrent theme from the interviews among providers was that identification for

Table 3 *Clostridium difficile* infection (CDI) knowledge scores overall, by healthcare provider, and each CDI knowledge category

CDI knowledge sorted by healthcare provider					
		Occupation			Overall
		Nurse ($n = 11$)	Physician (n = 11)	Pharmacist ($n = 4$)	All participants ($n = 26$)
Median Score (0–7), [1st, 3rd interquartile]		1 [0, 2.5]	5 [4, 6]	0.5 [0, 1]	3 [0.25, 4.75]
Knowledge Classification, n (%)					
No		6 (54.5)	0 (0.0)	4 (100.0)	10 (38.5)
Limited		4 (36.4)	0 (0.0)	0 (0.0)	4 (15.4)
Moderate		0 (0.0)	6 (54.5)	0 (0.0)	6 (23.1)
Advanced		1 (100.0)	5 (45.5)	0 (0.0)	6 (23.1)
Knowledge assessed in each CDI knowledge category					
Components of CDI knowledge assessment, n (%)					
1. Identification	1.1 Characteristics of bacteria	2 (18.2)	4 (36.4)	0 (0.0)	6 (23.1)
	1.2 Risk factors	3 (27.3)	10 (90.9)	0 (0.0)	13 (50.0)
	1.3 Signs and symptoms	3 (27.3)	11 (100.0)	2 (50.0)	16 (61.5)
2. Diagnosis	2.1 Diagnosis	1 (9.1)	10 (90.9)	0 (0.0)	11 (42.3)
3. Treatment	3.1 Treatment options	1 (9.1)	7 (63.6)	0 (0.0)	8 (30.8)
4. Prevention	4.1 Hand washing needed	4 (36.4)	7 (63.6)	0 (0.0)	11 (42.3)
	4.2 Need for contact isolation	4 (36.4)	8 (72.7)	0 (0.0)	12 (46.2)

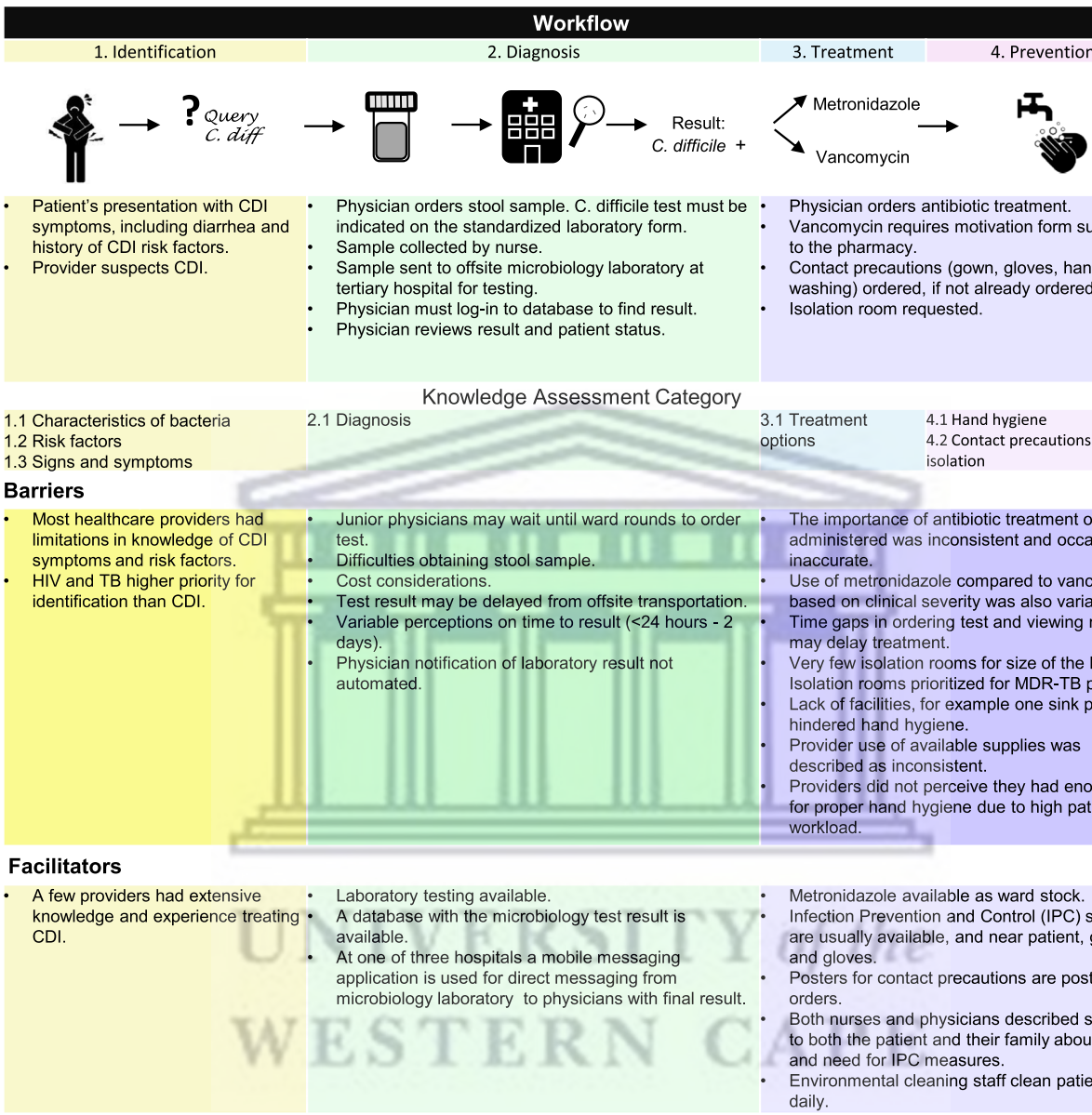

Fig. 1 *Clostridium difficile* infection (CDI) identification, diagnosis, treatment, and prevention workflow: facilitators and barriers

HIV and TB was prioritized over CDI. Physicians who have worked in the United Kingdom (U.K.) elaborated that the sense of urgency in South Africa for CDI was different than their previous experience due to competing attention of other prevalent disease.

> *"When I was in the UK [United Kingdom] years ago... [when] the manager mentioned C. diff the staff would jump up and down and get incredibly panicky... we just don't have that sense of urgency here... if you mention to someone in any hospital, they will go 'Okay, what is that?' [in cavalier tone]... however, if you tell them there is a patient with a potential XDR-TB [Extensively drug-resistant TB], then they may jump up and down. So the whole thing with C. diff it's a reality... ...a lot of people just think it's a disease with the elderly, but we have a lot of immunocompromised patients..."* - Physician

At one hospital, CDI awareness in senior staff only increased after an outbreak in the hospital. Awareness was lower for rotating junior staff who did not experience the outbreak.

> *"In terms of my junior staff, I think [CDI] ranks quite low. I think it's got to do with the way we've become*

aware last year. We've had more cases making us aware that it's highly infectious." - Physician

While some providers conjectured CDI to be a national problem, others did not, and no providers were aware of CDI magnitude in South Africa. Facilitating CDI identification were the senior providers with higher CDI knowledge. At one of the hospitals, an ASP was referenced as attributing to low incidence.

Diagnosis

After identification, to inform diagnosis, a stool sample from the patient is tested at a laboratory for *C. difficile*. While all hospitals in our study had laboratory testing available to conduct a *C. difficile* PCR test, testing occurred offsite as there was not capacity for the PCR test at the onsite laboratory. In order to test for *C. difficile*, physicians must indicate the test on a standardized laboratory form. Perception of time to result varied widely and was attributed to delays in initiating treatment. Additional barriers identified included staff difficulties obtaining stool samples due to staff shortages and non-standardized collection of laboratory samples. Laboratory test costs were occasionally cited as reasons to not test for *C. difficile*. Eleven interview participants described CDI diagnosis (42.3%, Table 3).

"Most of the time they are not tested, because they come from the emergency, and because our emergency is so busy, then the patient is pushed up to the ward. So then only when the patient is in the ward, and then we are actually reporting the [diarrhoea] to them [post call]. And then report that the patient is having diarrhoea; then that's the only time that they collect a stool specimen, and then after some, a couple of days, they get the results: the patient is positive. See... It could be about a week." - Nurse Focus Group

Other attributes identified in delaying the time to diagnosis include waiting for a physician to suggest the *C. difficile* test or until ward rounds to order it. To find results, physicians must proactively login to the database—usually from their personal mobile phones, as computer stations are not easily available. One of three hospitals uses a mobile messaging application for direct messaging from the microbiology laboratory to physicians with the goal of reducing the result notification time.

"I think the one resource that we've shown very well is the communication system. I think we chose the cheapest one we could find which is WhatsApp and that does make a difference in terms of managing your patients and getting a quicker diagnosis. The thing about WhatsApp is if a patient had a positive result, it would take the doctor another 2 days to figure it out that an infection exists. We actually have an alert system that works." - Physician

After observing the test result, the physician informs the nursing staff if the patient has a CDI. The IPC nurses are also informed of results and may, in turn, inform the medical team. However, there is not a timely and consistent pathway for this notification, especially during post-call hours. The IPC nurse sends physicians a report including positive *C. difficile* test results on a monthly basis.

Treatment

Antibiotic treatment options for antibiotic-associated diarrhoea included in South African treatment guidelines at the time of the interviews were oral metronidazole initially and oral vancomycin for diarrhoea not responsive to metronidazole; vancomycin must be oral to reach the infection. Of note, the interviews were conducted prior to the revised IDSA CDI guidelines in 2018 [3]. Eight (30.8%) respondents mentioned CDI treatment options, including treatment with metronidazole and vancomycin, though the importance of antibiotic treatment administered orally was reported inconsistently and occasionally inaccurately.

A few providers also discussed the clinical use of metronidazole compared to vancomycin, including patients' illness severity.

"So patients who don't respond to metronidazole would definitely be candidates for vancomycin or a metronidazole allergy." - Physician

Communication barriers were attributed to delays in treatment and included factors such as results being finalized while the physician was post call and drug order errors needing clarification.

Healthcare providers' high familiarity with metronidazole and its availability on the hospital floor as ward stock facilitated its use for CDI treatment. To order vancomycin and other antibiotics on the Essential Medicine List for Hospital Level Adults, providers needed to complete a pharmacy-approved motivation form that facilitates appropriate antibiotic use. Participants reported a time gap between ordering, sending the medication chart to the pharmacy, having the medication delivered to the ward, and administrating it to the patients. Some orders might be written up and not sent to the pharmacy. For stat orders, nurses may retrieve orders from the pharmacy. The pharmacies were closed during evenings and weekends. An emergency stock of inventory is kept in the emergency center. If the needed drug is unavailable, an on-call pharmacist is called-in to prepare it.

Occasionally medication was not administered and incorrectly documented as unavailable while drug was available in the emergency stock. Other reported barriers to patients receiving medications as ordered included: illegible handwriting, medication orders not including which ward an order came from, and physicians writing brand names when nurses only know the generic name. Additionally, sometimes a medication was given and not recorded; other times the patients missed doses because they were not present.

"The problem with this is ...that sometimes the results come back, the doctor is post call. Yes, and then he will only get the feedback the next day when he is actually coming to check on his patients. So that is the delay to start"- Nurse Focus Group

Prevention: Contact precautions, hand hygiene, isolation, environmental cleaning

Contact precautions CDI prevention procedures include contact precautions (e.g. gown, gloves) to reduce the risk of *C. difficile* spreading to other patients. Twelve (46.2%) participants reported the need for strict contact precautions when CDI was suspected or diagnosed. Supplies and procedures for IPC (included posters displaying orders for contact precautions) were usually available but not always utilised. Supplies (including gowns, gloves, masks, and hand sanitizer) were available in close proximity to a patient once contact precautions were ordered. Staff education and timely notification of need for infection control were the most common barriers to IPC measures. Pressure from patient bed shortages can lead to patients being placed near each other. Contact precautions with the first suspicion of CDI was described at one of the hospitals.

"...any patient with diarrhoea is placed with contact precaution; until we know if they have been exposed to any antibiotics, we put them as high risk." - Physician

At the three hospitals, the ward nurse in charge will enforce contact precautions with the nurses and the attending/consulting physicians will enforce junior physicians' contact precautions. The IPC team also enforces IPC practices. Both physicians and nurses inform patients about contact precautions; patients are told to inform their family members. While senior physicians reported informing patients of the need for IPC in the CDI setting, nurses considered themselves more approachable than the physicians and took a primary role in communicating with patients. One junior physician admitted his/her peers' shortfalling.

"I think that from all of it, that is where the biggest failing comes in—that we often don't tell patients enough of the stuff. So, I would like to think that once it's done there is a proper [communication] about the patient having things that can be transmitted, with words that they can understand and the importance of them not going around and touching lots of things and letting them know the reasons for gloving up and putting on gowns and stuff for their own peace of mind…It's apathy from the medical staff we forget to do these things..." - Physician

Hand hygiene Facilitators and barriers to hand hygiene were related to the treatment of patients with CDI and additional infections. Hand hygiene practices for patients with CDI should include hand washing with soap and water to remove *C. difficile* spores that are not killed by alcohol hand sanitizers. Supplies, including paper towels, soap, and hand sanitizer, were frequently available but not always utilised. Some stated that insufficient supplies were a barrier; others said that supplies were always available. Eleven (42.3%) participants acknowledged the importance of washing hands with soap and water when treating patients with CDI (Table 3).

"...have to use soap and water, we take [the] de-germ [alcohol based hand sanitizer] away from bedside so they are forced to use soap and water." - Physician

Some perceptions regarding this important hand hygiene practice were inaccurate.

"I would not say a normal hand soap is better for C. diff*, I would say something alcohol based."* - Physician

Staffing shortages and high workload were described as reasons for inconsistent hand hygiene practices.

"Can I tell you, all over the basins is that sign [WHO's "5 Moments of Hand Hygiene"]… but we don't practice it...We don't follow five moments of Hand Hygiene. We follow it when we go home... You can't afford to take that 5 min." – Nurse Focus Group

Participants described hand hygiene events (e.g. ultraviolent light, blue soap) in their hospitals that encouraged effective hand hygiene. Many stated that overcrowding and lack of facilities (e.g. one sink per ward) hindered hand hygiene as well as: the high ratio of patients to nurses, education limitations, and sometimes-empty alcohol and/or soap dispensers.

Isolation Infrastructure limitations were a major barrier to IPC, often preventing CDI patients from allocation to an isolation room. Isolation room availability ranged from two to four rooms. Isolation rooms were specifically prioritized for multidrug resistant tuberculosis (MDR-TB) patients, who may occupy the room for a month. CDI is viewed as a lower priority for isolation rooms.

> *"The fact that we have got a lot of immunocompromised patients in terms of our HIV rates and TB rates, a lot of our patients are at risk due to the use of antibiotics. In the UK we used to see a lot of elderly patients, but here you have got a different spectrum of patients, so C. diff is a huge risk… I think everyone focuses on MDR and very few people actually focus on C. diff … C. diff is not something that is high on the radar."* - Physician

Challenges for IPC included patient education regarding IPC, especially patients leaving isolation, walking around the hospital, and using shared bathrooms.

> *"The big problem that we have in our wards is a lack of isolation facilities. For an entire hospital, we've got only four isolation rooms [that] do not include isolation bathrooms. So a C. diff patient would have to use the same toilet as other patients."* - Physician

Both nurses and physicians described speaking to patients and their family members about isolation. An elevated desire from patients to understand their condition was expressed when patients were moved to an isolation room.

> *"Sometimes you'll find the patient doesn't know what is going on, but when you move them into an isolation room then they want to know why."* - Nurse

Environmental cleaning The ward managers inform cleaning staff verbally about room cleaning needs. Under supervision, the cleaners complete a written checklist for the bathrooms and patient rooms. Cleaning is sometimes rushed due to high bed demand, and the staff nurses will help.

> *"It's just that we are busy so the beds are always in demand so sometimes there is no opportunity for cleaning because everything is rush, rush, rush, rush. When the patient is waiting on discharge, others are waiting for that bed so we don't have the opportunity to do the spring cleaning of the unit. We aren't always able to do it in a calm environment."* – Nurse

Section II: Organizational Culture

Themes related to organizational culture (beliefs and attitudes) and how leadership and administration respond to new ideas, specifically 'change culture', were analyzed in order to inform future interventions. Through this coding an additional organizational culture theme emerged related to healthcare provider responsibility and accountability.

Change culture: how leadership and administration respond to new ideas

The majority of respondents described leadership as being supportive of new ideas. Some respondents did not feel leadership was supportive of bottom-up ideas; others believed that ideas with evidence of positive impact would be supported. A few respondents noted a barrier to change related more to nursing staff and junior physician turnover than to administrative support. Progressive change is difficult when the same education concepts are repeated with rotating healthcare providers; institutional memory regarding CDI and CDI management was lost.

> *"Implementing change and practical change are very different, so we are able to change our practice so we can make lots of suggestions... but the difficulty comes in that our staff [is a] rotating staff."* - Physician

A nurse new to a leadership position anticipated facing challenges in changing long-standing practices.

> *"The people above me, the specialist physicians or consultants, are quite open to change. If you can show clearly that an idea is going to work, the department is open to change and improving things. As you get higher up the leadership chain, it becomes more difficult to introduce change. I do find that on the face of it, the managers seem to be okay and accepting and are happy to listen."* - Physician

Responsibility and accountability

While the interviewees described achievements of and challenges for patients and healthcare providers following IPC precautions, low adherence emerged as a compelling theme—sometimes in the context of IPC in general and for the treatment of TB, particularly when participants had limited CDI knowledge. Perception of the threats from infectious diseases and IPC prioritization also appear to be barriers to adherence when supplies are available. Accountability structures are not in place to properly encourage providers to remain knowledgeable about guidelines nor enforce IPC precautions.

"It seems we have many awareness days… we had spike last year, 2 years ago… we have had quite a few staff members contracted tuberculosis… people only get aware if their buddy gets it… It makes it real." - Physician

"Just to get the doctors to wear gloves—that for me is another thing where I can just say… like, 'Why are you not wearing gloves?' or, just tell them 'Your patient has TB. Can you put on your mask please?' …together with the hand washing, and at the end of the day, it is part of the IPC principles to have full personal protection equipment available in the unit, but there's hand sanitizers, soap, and water, available in the unit, so no one has an excuse." - Physician

Informal structures for peer accountability were discussed as a helpful strategy from two interviews. First, accountability for hand hygiene occurred on the ASP ward round at one hospital. Second, an Operational Manager in the Operating Room (Theater) described nursing and cleaning staff who speak up about needs and follow cleaning expectations.

"The cleaning staff and the nursing staff is quite well informed as to what is supposed to happen, because sometimes they can tell you. 'Sister, this was not done yet; You can't really put your patient here'… Those are the people that I work with... that I come across, that will tell me. Doesn't matter if you are the cleaner, you can tell me, 'Sister, it's not ready yet.' You understand. It's that relationship that we have [of a] multidisciplinary team, to do what is expected of us." – Nurse

Discussion

Principal findings

This is the first qualitative study of CDI in Sub-Saharan Africa, and the results provide novel insight into CDI treatment and workflow in a limited resource setting. The context of CDI in Africa is especially important to consider given the high HIV and tuberculosis prevalence and high risk of *C. difficile* associated mortality in this population. This study reveals significant barriers and facilitators to CDI treatment in public district (secondary) level South African hospitals. Major barriers included knowledge gaps in CDI management, especially regarding awareness of the infection, transmission, treatment, and IPC practices among health care providers. Physician CDI knowledge was higher than nurse and pharmacist knowledge. The results reveal opportunities for healthcare provider education related to CDI. Our study affirms that healthcare providers have an awareness of evidence-based IPC precautions but barriers to following them include perceptions of priority and time availability.

Implications: perceptions and knowledge

Based on quantitative results from the overall CDI knowledge assessment, participants had limited CDI knowledge. Gaps in CDI knowledge may delay clinical suspicion and all workflow steps in CDI identification, diagnosis, treatment and prevention. While physicians scored higher, some physicians were less confident regarding when to order the *C. difficile* test resulting in delayed diagnosis. Physicians with high CDI knowledge noted an urgency surrounding CDI not observed in junior physicians and other healthcare providers.. This, together with a high risk of mortality in patients with positive *C. difficile* test results, underscores an urgent need for education and intervention tailored to relevant aspects of healthcare providers' job responsibilities.

Overall, participants scored well in areas of identifying CDI risk factors, signs, and symptoms. However, improvement is needed in terms of educating healthcare professionals in South Africa about other aspects of CDI. In the occupation subgroup analysis, nurses and pharmacists appear to be less knowledgeable about CDI characteristics, with response rates of 50% or less in all the knowledge assessment categories. The identified areas for potential development relevant to nurses and pharmacists are: CDI patients' need for contact isolation, the importance of hand washing instead of using alcohol gel in preventing the spread of CDI, and CDI treatment options. Nurses can also be educated to suspect CDI when monitoring bowel movements.

This study reveals a more complicated process for obtaining and administering vancomycin compared to metronidazole that may be hindering healthcare providers' use of vancomycin. In an epidemiology, treatment, and outcomes study in the same setting, vancomycin was rarely ordered (2%) as initial CDI treatment [4]. One strategy is to incorporate treatment options for CDI into pharmacist education and teach pharmacists what to look for on physician-submitted motivation forms. Pharmacist education about treatment options is especially important considering the role pharmacists have in the approval process for vancomycin use. The healthcare team should be educated on the clinical use of vancomycin for CDI with an emphasis on timely preparation and delivery.

How results relate to other studies

Our study affirms current literature's described need for improved CDI identification in settings with extensive CDI experience. Despite a history of substantial CDI outbreaks in Europe, a study identified persistent underdiagnoses of CDI when all diarrhoea samples were tested at 482 hospitals across 20 European countries; 23% of *C.*

difficile positive results were not identified at the local hospital. Authors attributed the underdiagnoses to a lack of clinical suspicion and suboptimal laboratory diagnostic methods [9]. Meanwhile, in the US, a regulatory climate that reduces hospital reimbursement for patients who develop hospital-acquired infections is driving efforts to refine testing protocols to avoid *C. difficile* over testing and inappropriate diagnosis [10]. These studies emphasize the importance of appropriate testing for diagnosis.

A global review of CDI guidelines found antimicrobial stewardship (ASPs) to be universally recognized as an essential evidence-based component of CDI IPC [5]. Continued development of interdisciplinary ASPs in limited resource settings is necessary to facilitate effective CDI management and IPC measures.

One barrier to hand hygiene identified in this study was the perception that there is insufficient time available for thorough hand cleaning. Indeed, in a study conducted in the US about healthcare providers' compliance with IPC practices for patients with CDI, full compliance was very low and time-consuming with a mean time for full compliance greater than 5 min for patients in single isolation rooms [11]. Patient care workload continues to be a barrier to full compliance with CDI contact precautions in high resource settings [12]. Therefore, improving full compliance of IPC practices in limited resource settings will require both a workload adjustment to allow more time per patient and education on the importance of CDI-related IPC practices.

Significant challenges for the implementation of IPC programs and practices exist in low and limited resource settings, including infrastructural constraints with a limited number of isolation rooms and variable staff compliance with hand hygiene practices. A similar qualitative study in India found perceived workload and nursing staff turnover to be barriers to infection control [13]. This relates to our study's previously referenced finding that perceived workload hindered infection control practices, especially regarding hand hygiene. Our respondents reported high turnover of both nursing staff and junior physicians as barriers to implementing change. The secondary hospitals included in our study did not have an IPC team as developed as the one in the tertiary hospital in India. The study in India also found participants reporting the availability of IPC supplies but experiencing challenges with compliance, while an international study of healthcare settings representing 30 countries identified inadequate supplies as a barrier to infection control of multidrug resistant organisms in some high and middle income countries [13, 14].

Limitations

As a qualitative study, the results are not generalizable to a larger population but may be transferable to similar settings. Visiting researchers' presence conducting the interviews may have affected responses; stated practices are not necessarily the reality of practice. While all interviews were conducted in English, English was a second language for some participants. This may have limited the respondents' understanding of some questions and ability to articulate responses. Furthermore, we may have underestimated facilitators to CDI management in an attempt to identify improvement opportunities. Our analysis was not a systematic audit of workflow and practices, and some inaccuracies may exist. To mitigate bias, multiple researchers of the study team reviewed the results. Finally, as we developed the knowledge assessment after the interviews were completed, the assessment is not yet validated and results are limited. Our knowledge assessment measured breadth of CDI knowledge and not depth. For example, some providers gave detailed explanations for some of the knowledge components, such as advantages of different testing protocols, yet these explanations were still only assigned one point for that component.

Conclusions

Our analysis provides a detailed description of the facilitators and barriers to CDI workflow, including the need for increased healthcare provider knowledge of CDI management. Interventions should increase CDI knowledge and utilization of the available systems and supplies by addressing the identified barriers and championing the identified facilitators. Increasing CDI knowledge alone is unlikely to be effective without addressing the need to create a sense of urgency around CDI and appropriate IPC practices. The results provide context for technical intervention and implementation strategies in low-resource public healthcare settings. This study serves as a baseline and supplements quantitative CDI patient data from ongoing CDI research including provider education and a clinical intervention to improve CDI quality of care in South Africa. The results of this workflow and provider knowledge analysis identify areas of need and are useful to design interventions to improve the quality of care for CDI patients in this population and similar limited resource settings.

Abbreviations

ASP: Antimicrobial stewardship programs; CDI: *Clostridium difficile* infection; IPC: Infection prevention and control; MDR(-TB): Multidrug resistant(–tuberculosis); PCR: Polymerase chain reaction; SEIPS: Systems Engineering Initiative for Patient Safety; TB: Tuberculosis; UK: United Kingdom; US: United States; XDR-TB: Extensively drug-resistant TB

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Availability of data and materials
De-identified interview transcripts are available on request from the corresponding author.

Authors' contributions
LL designed the study, designed data collection, monitored data collection for the whole study, conducted interviews, transcribed audio, analysed the data, drafted and revised the paper. SB provided guidance on the study and revised the paper. WR provided guidance on the study and revised the paper. NS provided guidance on the study and revised the paper. TE transcribed audio, analysed data, and revised the paper. KHP transcribe audio, analysed data, and revised the paper. RC facilitated the collaborative project between the University of the Western Cape and the University of Wisconsin, provided guidance on the study and revised the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the University of the Western Cape Department of Research Development, Ethics Reference Number: HS/16/1/24. Participants were provided an informed consent document approved by the ethics committee prior to the interview and could decline participation at any time.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Author details
[1]University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, WI 53705, USA. [2]University of the Western Cape School of Pharmacy, Robert Sobukwe, Cape Town 7535, South Africa. [3]University of Wisconsin School of Medicine and Public Health, 750 Highland Ave, Madison, WI 53726, USA.

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Appendix K: ***Antimicrobial Resistance & Infection Control*** **author guidelines**

Appendix K

Antimicrobial Resistance & Infection Control Author Guidelines

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Antimicrobial Resistance & Infection Control

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Submission Guidelines

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Laurel Legenza [a,b,*], Renier Coetzee [b,c], Warren E. Rose [a], Tasneem Esack [d], Kenneth Crombie [e], Megan Mina [e,f], Nasia Safdar [g], Susanne G. Barnett [a]

[a] University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, WI, 53705, United States
[b] University of the Western Cape School of Pharmacy, Robert Sobukwe, Cape Town, 7535, South Africa
[c] University of the Western Cape School of Public Health, Robert Sobukwe, Cape Town, 7535, South Africa
[d] Victoria Hospital, Wynberg, Cape Town, 7800, South Africa
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[f] General Justice Gizenga Mpanza Regional Hospital, KwaDukuza, KwaZulu-Natal, 4450, South Africa
[g] University of Wisconsin School of Medicine and Public Health, 750 Highland Ave, Madison, WI, 53726, United States

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ABSTRACT

Background: *Clostridioides difficile* infection (CDI) contributes the global threats of drug resistant infections, healthcare acquired infections and antimicrobial resistance. Yet CDI knowledge among healthcare providers in low-resource settings is limited and CDI testing, treatment, and infection prevention measures are often delayed. Objectives: to develop a CDI intervention informed by the local context within South African public district level hospitals, and analyze the CDI intervention and implementation process.

Methods: A CDI checklist intervention was designed and implemented at three district level hospitals in the Western Cape, South Africa that volunteered to participate. Data collection included a retrospective medical records review of patients hospitalized with *C. difficile* test orders during the 90 days post-implementation. Patient outcomes and checklist components (e.g. antibiotics) were collected. Qualitative interviews (n = 14) and focus groups (n = 6) were conducted with healthcare providers on-site. The Consolidated Framework for Implementation Research (CFIR) and the Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies (FRAME-IS) were applied to collected data and observations in order to identify drivers and barriers to implementation and understand differences in uptake.

Results: One of the three hospitals displayed high intervention uptake. Highly relevant CFIR constructs linked to intervention uptake included tension for change, strong peer intervention champions, champions in influential leadership positions, and the intervention's simplicity (CFIR construct: complexity). Tension for change, a recognized need to improve CDI identification and treatment, at the high uptake hospital was also supported by an academic partnership for antimicrobial stewardship.

Conclusions: This research provides a straight-forward health systems strengthening intervention for CDI that is both needed and uncomplicated, in an understudied low resource setting. Intervention uptake was highest in the hospital with tension for change, influential champions, and existing academic partnerships. Implementation in settings with fewer academic connections requires further testing of collaborative implementation strategies and proactive adaptations.

1. Introduction

Patients with *Clostridioides difficile* infection (CDI), can suffer from health outcomes that range from mild-to-severe diarrhoea to mortality, as well as experience costly hospitalizations and readmissions.[1–6] In addition to physical impacts, CDI impairs patients' psychological, social, professional, and financial lives.[7,8] CDI remains a global health threat with incidence in South Africa similar to Europe.[4,5,9–11] CDI hospital outbreaks may trigger changes in patient care protocols including closure of hospital wards to limit further transmission.[12–14] Quality CDI

* Corresponding author. 777 Highland Avenue, School of Pharmacy, University of Wisconsin-Madison, Madison, WI, 53705, United States.
E-mail address: Legenza@wisc.edu (L. Legenza).

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care requires timely identification, rehydration, antibiotic treatment, and use of infection prevention and control (IPC) measures to prevent devastating hospital outbreaks.[5,15,16] Measurable gaps exist in the delivery of these steps as well as CDI knowledge across healthcare providers in hospitals in the Western Cape, South Africa, and likely in similar low-resource settings.[17,18] CDI interventions developed and proven in high resource settings, where most CDI epidemiological and quality improvement studies are performed, may not apply directly to low resource settings.[9,19] There is a gap in CDI literature from low resource settings, especially sub-Saharan Africa, particularly in adapting CDI interventions to low resource settings.[9,20,21] Authors of a recent meta-analysis of CDI in developing countries concluded CDI prevalence in patients with diarrhoea (15%) is likely an underestimate due to inconsistent diagnostics, surveillance, and low awareness.[20] Thus, CDI interventions and the description for their implementation tailored to these local circumstances are urgently needed.

Implementation Science is a multidisciplinary research field and often aims to improve healthcare systems by optimizing the fit of evidence-based practices and interventions with implementation context.[22,23] It also aims to increase intervention reproducibility and transferability, and reduce the lag time between evidence generation and practice.[22–25] Yet, pharmacy has not fully integrated Implementation Science frameworks and strategies to enhance pharmacist-led interventions.[26,27] The Consolidated Framework for Implementation Research (CFIR) is a highly cited and adaptable meta-theoretical framework that excels in examining the interplay of contextual factors surrounding an intervention.[28] CFIR organizes theory and evidence-based constructs into five domains with a total of 39 constructs.[28] However, Implementation Science applications are lagging in low- and middle-income countries (LMICs).[29–31] Limited CFIR applications have been done in sub-Saharan Africa, primarily via academic partnerships in Kenya, Mozambique, and South Africa.[31–34] No prior work to our knowledge has leveraged implementation science to develop and explain a CDI intervention in South Africa.

The first objective of this study is to develop a locally-informed CDI intervention within South African public district level hospitals following implementation science principles. The second objective is to analyze the development of the CDI intervention, implementation process and implementation adaptations to understand differences in acceptance and uptake of the CDI intervention.[28,35] The study objectives were achieved; the methods describe steps for developing the intervention and conducting the CFIR analysis. The relevant CFIR constructs are presented in the Results. The Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies (FRAME-IS) is also utilized to provide a precise understanding of implementation adaptations.[36]

2. Methods

2.1. Overview

In this study, we designed and implemented a CDI checklist using strategies that were modified and adapted across hospital contexts. '*Intervention*' refers to the tool, a multicomponent CDI checklist in the form of a physical sticker with general diarrhoea management and CDI clinical interventions (Fig. 1). The implementation strategies included development of stakeholder relationships, intervention champions, and training sessions, which together are called the '*implementation package*' in this study. As noted, we are assessing both the intervention tool and the implementation strategies by examining intervention uptake - the use of the checklist and its effect on measurable CDI care provided, and CFIR constructs associated with uptake. Across three hospitals the intervention did not change, but the implementation package was modified and adapted at each hospital. Modifications to the champions implementation strategy were further detailed using the FRAME-IS.

2.2. Ethics and participating hospitals

This study received approval from the University of the Western Cape Humanities and Social Science Research Ethics Committee, Department of Research Development (Ethics Reference Number: HS/16/1/24), the National Health Laboratory Service, the South African National Department of Health Western Cape, and the participating hospitals. The four hospitals included in the baseline epidemiology study were invited to participate. All invited hospitals were public district level hospitals in the Cape Town metropole. Three hospitals

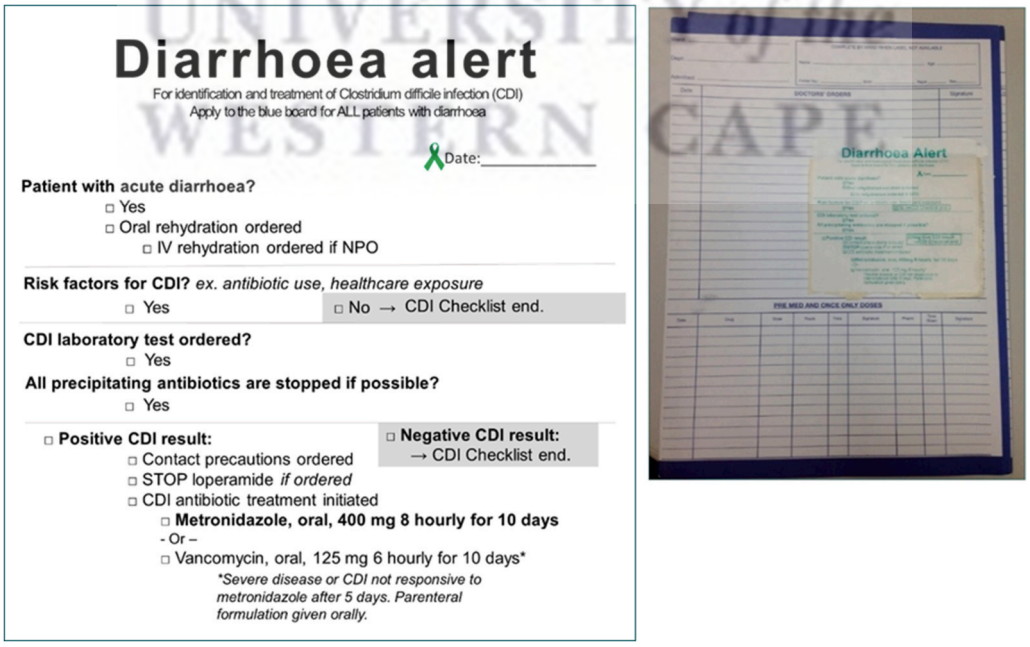

Fig. 1. CDI intervention checklist* and CDI checklist applied to medical record order form
*Treatment follows the 2015 South African Standard Treatment Guidelines in place at the time the checklist was developed. The 2019 guidelines now specify metronidazole for treatment of mild to moderate *Clostridioides difficile* infection (CDI) and vancomycin for severe infection.

accepted the invitation, volunteering to participate in the study intervention and implementation, and one hospital declined to meet with the research team at the time of implementation.

2.3. Setting

South Africa has the greatest income inequality in the world, and the urban area surrounding Cape Town is still marked by a deep history of racial segregation.[37,38] The South African Department of Health, the national health system, serves 84% of the population. Meanwhile the private sector serves those who can afford it, approximately 16% of the population.[39] The cost to use the public health system is adjusted based on income, embodying a right to healthcare approach.[40] District level hospitals, also known as secondary level hospitals, often provide care for complex patients suffering from human immunodeficiency virus (HIV) and tuberculosis (TB), and patients of all ages, including the elderly with chronic conditions.[41] The hospitals included in this research averaged 265 inpatient beds and had similar but limited government funded resources (e.g. paper health records). The South African Department of Health's organizational structure is similar to many public sector national health systems globally. Overall, the health system experiences many of the same challenges as other LMICs in Africa and globally, such as staffing shortages and overcrowding.[42] Healthcare professionals, including pharmacists, are unevenly distributed to the private sector.[43,44] Clinical pharmacy services are in very early stages or non-existent at many in public sector hospitals, but have advanced substantially in South Africa, especially in the private sector.[44–46] The tangible resources needed for CDI treatment (e.g. gloves, gowns, antibiotics, soap) are usually available within the hospitals. However, they are not always utilized, potentially due to knowledge gaps and/or a lack of awareness of the infection.[17,18]

The Western Cape Department of Health includes 237 clinics, 24 district hospitals, five regional hospitals, one tertiary children's hospital, and two tertiary adult hospitals. From expert and stakeholder feedback, we chose to base this research at the district level due to local need for understanding CDI and designing interventions.

2.4. Intervention and implementation

The intervention was identified and developed in four phases that mirror quality improvement principles and are an adapted version of the Plan, Do, Study, Act cycle.[47] The phases are summarized with Fig. 2. Details on the steps within each of these phases are presented in Table 1. The Expert Recommendations for Implementing Change (ERIC) strategies utilized are also named and further detailed in Table 2, including details on the stakeholders, healthcare providers and administrators, and pharmacy students engaged with this research.[35] The research team selected the initial ERIC strategies utilized in Step 1 informed by quality improvement training early in the project development. The topic area and specific project was selected by internal South African leaders, Department of Health administrators and healthcare providers (Table 1). The intervention and implementation package were determined collaboratively by the research team with input and advice from local stakeholders. During pre-implementation stakeholder engagement meetings, the plan for implementation was discussed. During these meetings the implementation plan was adapted to meet the level of interest and availability of personnel at each hospital.

Ultimately, the 'Diarrhoea alert' CDI checklist, was developed and implemented with education sessions informed by the local context. The checklist is shown in Fig. 1 with its application to the medical record order form. No modifications were made to the intervention between the hospitals; the intervention invariably maintained two core elements: the checklist and items on the checklist.

Post-implementation quantitative medical records data were collected and post-implementation interviews were conducted to assess the implementation and intervention effects. CFIR is the conceptual framework used to analyze study findings, including a description of the implementation process and CFIR constructs associated with use of the intervention or uptake.[34] Implementation strategy adaptations, including modifications to how the intervention was implemented (i.e. the implementation package), were documented with the new FRAME-IS, which both mirrors and builds on the original FRAME that documents intervention modifications.[36,48,49] We applied all seven FRAME-IS modules, including the optional modules, to the champions implementation strategy, as it was the most substantial implementation package modification between the three hospitals.

2.5. Data collection

Post-implementation a retrospective medical records chart review collected patient characteristics, CDI management, and outcomes (e.g., in-hospital mortality). Patient test results were collected from the National Health Laboratory Services. Medical records for patients hospitalized with a *C. difficile* test order during the 90 days following a 2-week implementation and training period were reviewed. Outpatient test results were excluded. The research team summarized collected data on the steps of CDI care provided and patient outcomes, which was later presented to each participating hospital through formal presentations and individual meetings as interest and schedules allowed. The post-implementation data collection followed the methods of the published baseline epidemiology and CDI management study.[18] Briefly, the outcomes and care measures included: oral and/or intravenous rehydration, contact precautions, use/discontinuation of contraindicated loperamide in patients with CDI, antibiotic treatments, infection prevention and control precautions, and in-hospital mortality.

Post-implementation semi-structured qualitative interviews were conducted with individual health care providers at Hospitals 1 and 2: nurses (n = 2), physicians including medical directors and administrators (n = 7), pharmacists (n = 2), nurse managers (n = 2), and IPC nurses (n = 1). Focus group discussions were also conducted with available nurses on hospital wards (n = 6 focus groups, ~4–9 nurses/focus group). Audio files (N = 20) from these interviews were transcribed verbatim, and two researchers coded the transcripts a priori to CDI workflow steps, feedback on the intervention, and the implementation process.

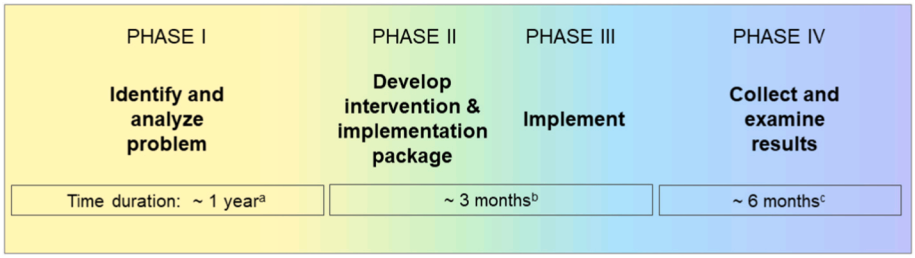

Fig. 2. Study design in four project phases
a. Estimated total time includes time to develop protocol and obtain research ethics approval. b. Estimated total time on site at hospitals preparing and implementing intervention. c. Estimated total time collecting and analyzing 90-day post-implementation results; does not include preparation of publication.

Table 1
Project phases with steps outlined from problem identification through results.

PHASE I: Identify and analyze problem		
STEP 1	Stakeholder engagement and identification of CDI need in South Africa	The innovation area, Antimicrobial Stewardship (AMS), was selected by internal South African leaders, Department of Health administrators and healthcare providers. Subsequently a 'Strengths, Weaknesses, Opportunities, and Threats' or SWOT analysis of AMS projects was conducted, and CDI was selected as the specific project due to the scarcity of available data on CDI at the district level in the Western Cape province. A mixed-methods research protocol was developed and approved.
STEP 2	Pre-intervention retrospective review of CDI patient care and outcomes	An CDI epidemiology and outcomes study was conducted to serve as baseline data for the intervention and provide data on the magnitude of CDI in public district hospitals in South Africa. Identified opportunities to improve patient care are also included in the published outcomes study.[a]
STEP 3	Stakeholder engagement on CDI	Pre-intervention qualitative interviews and observations mapped CDI workflow, including steps to identify, diagnose, treat, and prevent CDI, with identified barriers and facilitators to CDI care.[b] Interviews and focus groups gleaned information about what resources already existed and what elements of a CDI intervention would be both possible and helpful.
PHASE II: Develop intervention and implementation package		
STEP 4	Consideration of local context and synthesis of data to develop the intervention and implementation package	Local context gathered through **Phase I** of the project informed the intervention and implementation package. Elements of interventions already successful in the participating hospitals and feedback from both local stakeholders and infectious diseases leaders were considered. A literature review of existing checklists and bundle interventions globally for CDI was performed. The synthesis of these results led to the development of the intervention, the 'Diarrhoea Alert,' or CDI checklist, and implementation package, including tailored education sessions.
PHASE III: Implement		
STEP 5	Put into practice the intervention and adapt implementation package	We continued to adapt the implementation package for the intervention created in Step 4 to meet the local environment at each hospital based on feedback from local healthcare providers. Implementation at Hospitals 1 and 2 began with a trial of the training session at Hospital 1 delivered by the lead researcher, continued with adapted training across hospital wards and departments, and concluded with local champions, or individuals who dedicated themselves to the intervention and conducted follow-up. A more independent implementation model was utilized at Hospital 3 in order to see the effect of a train-the-trainer model for the project. The lead researcher trained a local champion to lead intervention implementation. Finally, implementation at Hospital 4 did not occur until after results from Hospital 2 were presented to Hospital 4 leadership.
PHASE IV: Collect and examine results		
STEP 6	Post-implementation engagement and interviews	Post-implementation interviews and focus groups were conducted to gather qualitative data about the efficacy of the intervention (i.e. how was the checklist being used or not, how were patients with diarrhoea and CDI being managed, what did the providers know about CDI post implementation) and feedback for future adaptations. Participants were recruited with purposive sampling of both providers who were previously engaged with intervention implementation and providers unfamiliar to the research team. An informed consent document, approved by the ethics committee, was provided to participants, participants provided written consent, and participants could decline participation at any time.
STEP 7	Preparation of qualitative data	Twenty interview audio files were transcribed verbatim, and two researchers coded the transcripts a priori to CDI workflow steps, feedback on the intervention, as well as the implementation package. The qualitative data analysis software NVIVO (Version 11, QSR International) was used for coding. Discrepancies in coding were discussed and resolved.
STEP 8	Preparation of results, CFIR[c] framework application, and FRAME-IS[d] application	The focus of this analysis: the CDI intervention development, implementation process and adaptations were analyzed to understand differences in acceptance, uptake, successes, and failures of the CDI intervention.

[a] Legenza et al. *BMJ Global Health* 2018.
[b] Legenza et al. *Antimicrobial Resistance and Infection Control* 2018.
[c] Damschroder et al. *Implementation Science* 2009.
[d] Miller et al. *Implementation Science* 2021.

The research team was available for questions from the local implementation leads at Hospitals 2 and 3 before, during and after the 2-week implementation and training period. The research team maintained communication with the local implementation leads at Hospitals 2 and 3 to answer questions and collect information regarding their experience and the intervention status via in-person meetings, text messages, emails, and phone conversations. Note, implementation at Hospital 3 occurred after post-implementation interviews at Hospitals 1 and 2.

2.6. CFIR analysis: preparation of results and CFIR framework application

A CFIR analysis was conducted with the following steps. The research team pragmatically applied the CFIR framework to results from the qualitative interviews, observations by research team members, and quantitative patient outcomes data in order to identify drivers and barriers to implementation and to understand differences in uptake at the three sites.[50]

The research team chose a qualitative approach to the CFIR analysis

Table 2
ERIC[a] implementation strategies used to develop the intervention and implementation.

Strategy	Actions taken
Develop stakeholder interrelationships	
Conduct local consensus discussions & needs assessments (Table 1, STEP 1)	Conducted a country-wide qualitative needs assessment of the South African health system via 1.) scoping review of policies and published literature to identify national priorities, and 2.) discussions with stakeholders and providers at policy, administrative, supervisory, operational, managerial, and patient care levels. Antimicrobial Stewardship was chosen as the innovation area by those who conducted the needs assessment. Consulted with academic leaders at various universities across South Africa and in Cape Town. Narrowed needs assessment to the Western Cape province level. Consulted with stakeholders at policy level regarding needs in both public and private sectors (e.g. Pharmacy Services, Western Cape Department of Health). Consulted with both infectious disease leaders in public and private sectors (e.g. South African Department of Health, private sector heads of microbiology). Consulted with internationally recognized infectious disease researchers and clinicians in South Africa and the United States, including those leading work in Antimicrobial Stewardship and *Clostridioides difficile* infection (CDI). Presented chosen problem (CDI) to leaders previously engaged in needs assessment and departments of internal medicine to affirm chosen problem was important and determine if clinical innovation to address it was appropriate.
Build a coalition (STEPS 1, 3, 4)	High-level hospital chief executive officers and administrators were engaged for project approval with the intervention. Heads of departments and managers assisted with introductions to the "educationally influential" and local opinion leaders to recruit and cultivate relationships with partners in implementation effort.
Conduct educational meetings & Inform local opinion leaders (STEPS 3,4)	Conducted pre-intervention interviews and meetings with "educationally influential" hospital administrators, senior physicians, infection prevention and control nurses, nurse educators, and pharmacy managers to teach them about the intervention as well as local opinion leaders with hope that they would influence colleagues to adopt the intervention.
Identify and prepare champions (STEP 5)	Identified and prepared champions at each hospital who would "dedicate themselves to supporting, marketing, and driving through an implementation, overcoming indifference or resistance that the intervention may provoke in an organization."[a]
Develop academic partnerships (STEPS 2–7)	Strengthened existing academic partnership between the participating Schools of Pharmacy. Engaged pharmacy students from both universities for shared training and skill-building with the research project, including partnership with the 1-year longitudinal research program for final year South African pharmacy students (two groups of students over two years) and inclusion of independent study and Advanced Pharmacy Practice Experience (APPE) students.
Use evaluative and iterative strategies	
Conduct local needs assessment (STEPS 1,2)	Conducted baseline CDI management and patient outcomes retrospective review including in-hospital mortality and identification of gaps in treatment and infection control.[b]
Assess for readiness and identify barriers and facilitators (STEP 3)	Identified barriers and facilitators through qualitative interviews with healthcare providers and stakeholders.[c]
Audit and provide feedback (STEP 5)	Visited hospital wards during implementation to audit use of the innovation and provide feedback to clinicians.
Train and educate stakeholders	
Develop educational materials (STEPS 4,5)	Developed training handouts and references/reminders. Developed educational reminder/ recognition wearable buttons.
Distribute educational materials (STEP 5)	Delivered educational materials in person during training and education sessions.
Make training dynamic (STEPS 4,5)	Tailored training to each healthcare profession (nurses, pharmacists, physicians). Included dynamic interactive learning delivery with open-ended questions and patient examples in training. Included examples to show when to apply the intervention that encouraged participant engagement in each stage of infection identification, diagnosis, treatment, and prevention. Provided in-person reinforcement follow-up training in the ward and asked about current patient needs (patients with diarrhoea). Provided training individually to any providers who missed initial group training sessions.
Support clinicians	
Remind clinicians (STEP 5)	Developed reminder posters for the intervention that were posted in the wards to prompt clinicians to use the intervention for applicable patients.

[a] Powell et al. *Implementation Science* 2015.
[b] Legenza et al. *BMJ Global Health* 2018.
[c] Legenza et al. *Antimicrobial Resistance and Infection Control* 2018.

to produce translational results and a reproducible description of the intervention and implementation package, while continuing to strengthen collaborative partnerships with community stakeholders.[51] Producing robust numeric ratings was not a priority of this project and thus not performed. The relevance of the CFIR constructs was determined following a multi-step filtering and assignment process.

First, LL reviewed all 39 CFIR constructs, including the "Detailed Description" and "Codebook Guidelines" as available at the http s://cfirguide.org/constructs/ website and then described in narrative and outline form the relevance of each applicable construct. Constructs that were non-applicable were excluded. Considering the data available and feasible scope of this study we chose to focus on three CFIR domains: 1) the Intervention, 2) the Inner Setting, and 3) the Implementation Process. The Outer Setting was not analyzed because all hospitals were affected by the same complex socio-cultural history, national politics, and Department of Health provincial- and national-level policies. The project was designed as a system-level intervention and was not intended for individual level analysis. Thus, the Individuals Involved domain was not analyzed. Finally, LL and RC discussed these methods and construct results.

In the second CFIR analysis step, constructs from the CFIR domains Intervention, Inner Setting, and Implementation Process were assigned to high or moderate relevance categories. Moderate constructs with overlapping findings were consolidated to the most pertinent construct. Constructs with low relevance were excluded. TE provided feedback on this construct list, relevance assignments, and drafted descriptions,

emphasizing aspects of construct details. The 'Planning' construct was then excluded as the key aspects were described in other more substantiated constructs.

Third, adjustments in the relevance assignments were made. Specifically, during subsequent iterative drafts of the manuscript, the following construct changes were made:

- Intervention: Complexity was moved to highly relevant and Evidence Strength and Quality was moved to moderately relevant;
- Inner Setting: Leadership Engagement was added;
- Implementation Process: Reflection and Evaluation construct, originally unassigned, was designated as highly relevant to complete the description of the implementation.

In this way, constructs that were unique to this intervention and those that described the intervention's level of uptake between hospitals remained in the highly relevant category. No other changes were made to the relevance distinctions. For the sake of focus and brevity, moderately relevant CFIR constructs were presented in the results table with further details explained in the **Appendix**.

Ultimately, findings were reviewed by all co-authors, including local

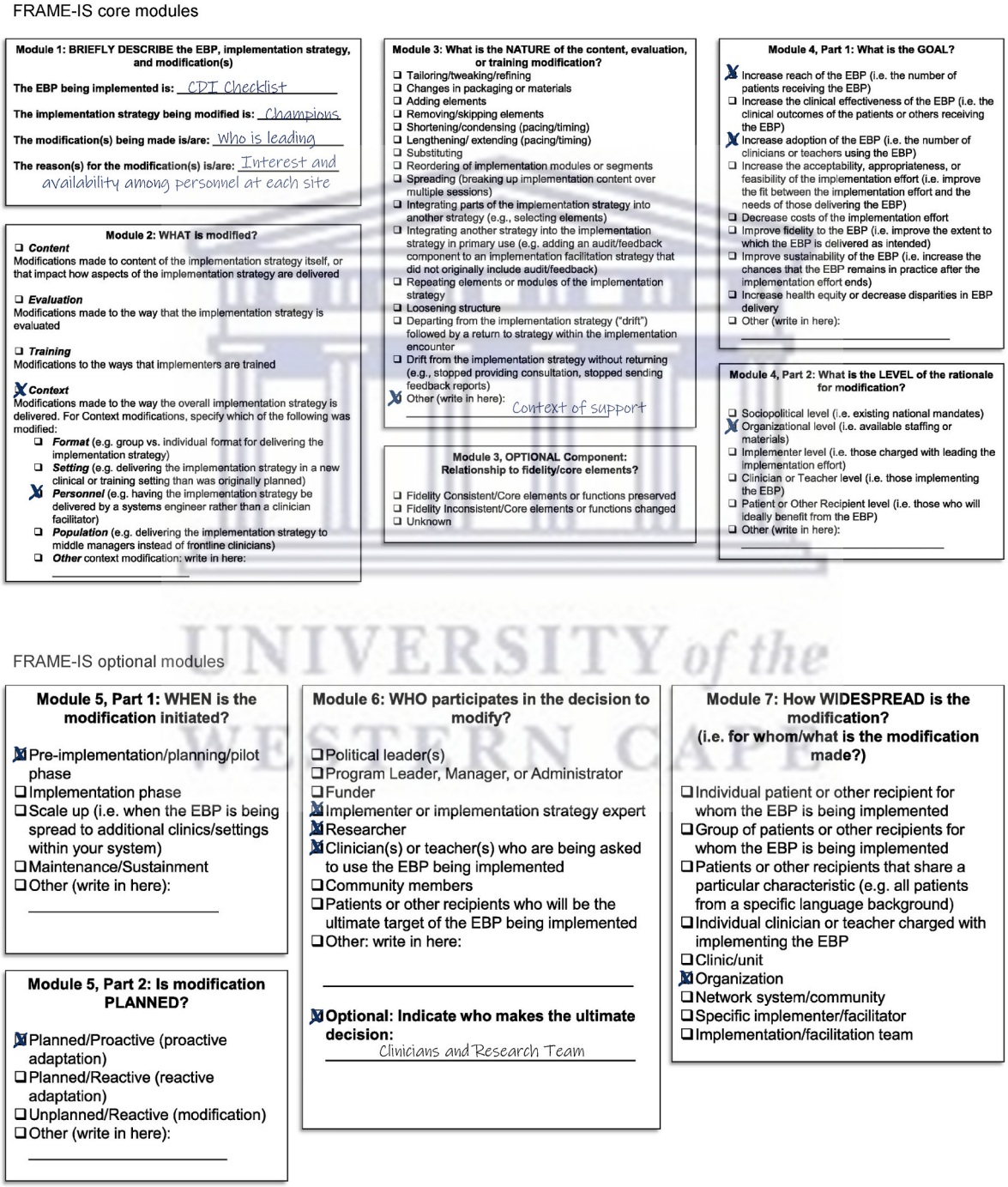

Fig. 3. Adaptations to the champions implementation strategy contextualized within the Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies (FRAME-IS)[a].
a. Applied FRAME-IS adapted from Miller et al. *Implementation Science* 2021.

Table 3
Intervention, Inner Setting, and Implementation Process highly relevant and moderately relevant CFIR constructs.

Relevance	Construct	Theme
CFIR Domain: Intervention		
High	Adaptability	We adapted existing evidence-based CDI interventions and checklists to fit the local healthcare setting and resources available.
High	Complexity	The simple intervention avoided altering standard work processes, and instead simply triggered reminders to identify patients with diarrhoea, provide quality of care measures, test patients at risk for CDI, treat patients with CDI, and apply IPC procedures. Physically applying the checklist sticker to the blue boards of patients with diarrhoea was the most complex step.
High	Source	Internal South African leaders and local healthcare providers selected the innovation area via a participatory process.
Moderate	Evidence Strength and Quality	Awareness and perceptions of evidence-based CDI interventions and other bundle approaches varied among healthcare providers.
CFIR Domain: Inner Setting		
High*	Leadership Engagement	All three sites required engagement of the hospital Chief Executive Officer or another executive-level representative before implementing the project. Hospital 2 leadership showed the strongest commitment. The Hospital 1 executive leadership welcomed the intervention and appreciated its value but expressed some skepticism on the long-term sustainability. At Hospital 3, attempts to meet with consultant level physicians were sometimes unsuccessful; meeting requests were declined, ignored, and/or canceled at the scheduled time of meeting.
High	Tension for Change	Hospital 2 leaders uniquely recognized the need to improve CDI identification and treatment.
High	Relative Priority	Providers prioritized TB and HIV above CDI. Concurrent IPC programs, such as hand hygiene trainings, lacked organization wide support.
Moderate*	Structural Characteristics	The social structure of the district hospitals included is similar to other public district level hospitals across Africa and other low resource healthcare settings. Uniquely, a weekly Antimicrobial Stewardship (AMS) ward round occurs at Hospital 2 and includes pharmacy and medicine presence along with trainees. The AMS ward round is often led by an infectious diseases expert from the tertiary teaching hospital/university.
Moderate*	Networks and Communication	The Department of Internal Medicine at Hospital 2 uniquely had a WhatsApp communication system for laboratory results, patient needs, and program reminders, including reminders about the CDI intervention.
Moderate*	Available Resources	Time and the personnel involved with the project were resources that varied for the implementation at each hospital. Tangible resources available, such as medications, IPC supplies (gloves, gowns, soap, etc.), and other supplies were similar at all publicly funded district hospitals.
Moderate	Access to Knowledge and Information	The barriers and facilitators study identified limited CDI knowledge as a major barrier to CDI treatment. The implementation process included CDI education and training materials in a digestible format. These materials, handouts, reminder posters, and the in-person training sessions on the ward or other convenient locations were similar across sites.
CFIR Domain: Implementation Process		
High	Engaging: *Stakeholders*	The stakeholder engagement process was most similar between Hospitals 1 and 2. At Hospital 3, the external researcher started stakeholder engagements (interviews) and trained a pharmacy intern to continue engagements (training).
High*	Engaging: *Opinion Leaders and Champions*	Opinion leading Hospital 2 physicians uniquely influenced the intervention uptake.
High	Reflecting and Evaluating	An increase in CDI testing and awareness observed in post interviews indicates that there was an increase in CDI knowledge due to the implementation package. The lead researcher presented results at Hospitals 1 and 2 in person via formal individual and group discussions and presentations. Results at Hospital 3 were presented to the Western Cape Department of Health as part of the internship program. Results from Hospital 2 were also presented to the Department of Health and Hospital 4 during an invited presentation to hospital leadership.

* Uniquely distinguishes the hospital with high intervention uptake (Hospital 2) and differences between the three hospitals.

healthcare providers from the participating hospitals. The Standards for Reporting Qualitative Research (SRQR) were reviewed as a checklist for describing our qualitative research.[52] This study presents the relevant pre- and post-implementation feedback and post-implementation findings within the FRAME-IS and CFIR frameworks to frame the intervention development and explain the implementation process.

3. Results

Uptake or adoption of the checklist intervention was highest at Hospital 2, and low at Hospitals 1 and 3. Differences in adoption were apparent from the qualitive interview data, conversations with implementation leads, and the retrospective review of patient records with *C. difficile* test orders during the 90-day post-implementation phase. Detailed outcomes from Hospital 2 are in the Appendix: Reflecting and Evaluating.

3.1. Implementation strategy modifications and adaptations with FRAME-IS

The implementation package consisted of the strategies detailed in Table 2, under the categories: Develop stakeholder interrelationships; Evaluative and iterative strategies; Train and Educate Stakeholders; and Support Clinicians. The implementation package was adapted at the three participating district level hospitals. Training sessions were led by the implementation lead(s) and adapted to resources, available and interested personnel at each hospital.

Project implementation leads were appointed by the organization and research team for the project based on available resources and interest (external lead researcher at Hospital 1, registrar and student at Hospital 2, pharmacy intern at Hospital 3). The 'who, what, when, and why' of these modifications to the champions implementation strategy are named with the FRAME-IS (Fig. 3). In this study the implementation leads served as champions; however, organizational support to empower the champions to lead, and their ability to drive through the intervention and overcome resistance varied between the hospitals.

Training at Hospitals 1 and 2 was performed by the external project lead. At Hospital 2, a medical registrar (medical resident) and medical student took roles of local peer champions. The adaptation to include a registrar proved to be the most effective and key differentiating factor.

For implementation at Hospital 3, the lead researcher trained a local champion to lead intervention implementation and provide the training sessions. The lead researcher and this local champion conducted the first education and intervention training at one of the hospital wards together. The local champion completed the intervention implementation at Hospital 3 as a project for a 1-year pharmacy internship through the Department of Health with guidance from the research team. However, gaining internal physician support was challenging. Additional details regarding the training sessions and adaptations are described in the Appendix, Supplemental detail on training adaptations and CFIR constructs.

3.2. CFIR construct results

This study uses the CFIR framework's replicable language to describe the intervention and results as well as to understand instances of high uptake and acceptance juxtaposed with resistance at hospital and individual levels. Highly relevant and moderately relevant constructs for the Intervention, Inner Setting, and Implementation Process are presented in Table 3 and summarized in Table 4. Moderately relevant constructs and additional details on select highly relevant constructs are provided in the **Appendix**.

As stated in the methods, the results present the CFIR constructs most relevant and differentiating to the intervention and implementation. Highly relevant constructs are detailed here.

I. Intervention/Innovation

3.2.1. Adaptability, complexity and source

The specific checklist implemented in this study was informed by existing CDI checklists and input from internal stakeholders, including local healthcare providers, hospital administrators, and local students.[53] The research team designed the intervention to fit the local healthcare setting and resources available, and address the gaps in CDI management described elsewhere.[17,18] An intervention sticker for TB was already in use and appeared to work well in the public hospitals. The CDI intervention was adapted to be applied to the medical chart orders page, or 'blue board,' of all patients with diarrhoea. While initially designed as the 'CDI Checklist,' the research team later changed the name to 'Diarrhoea Alert' to prompt a screening of all patients with diarrhoea. The checklist served as an alert and simple job aid for the elements of quality CDI care (Fig. 1; see Intervention constructs in Table 3 and further construct details in the **Appendix**). With CFIR, complexity is the construct that corresponds to this intervention's simplicity. Across sites, health care providers liked the checklist design and often reacted during trainings and interviews that it was really 'quite simple.' The CDI antibiotic treatment recommendations were based on the 2015 South African Standard Treatment Guidelines in place at the time of development.[54] The revised guidelines released in 2020, recommend metronidazole for mild-moderate CDI and vancomycin for severe CDI.[15]

The intervention source and development are detailed in the methods and appear with ERIC implementation strategies in Table 2. The implementation package consisted of the strategies detailed in Table 2, under the categories: Develop stakeholder interrelationships; Evaluative and iterative strategies; Train and Educate Stakeholders; and Support Clinicians.

Table 4
Identified CFIR constructs with moderate or high relevancy to implementation.

	CFIR Domain		
Relevancy	Intervention	Inner Setting	Implementation Process
Highly Relevant	• Adaptability • Complexity • Source	• Leadership Engagement • Tension for Change • Relative Priority	• Engaging: Stakeholders • Engaging: Opinion Leaders and Champions • Reflecting and Evaluating
Moderately Relevant	• Evidence Strength and Quality	• Structural Characteristics • Networks and Communication • Available Resources • Access to Knowledge and Information	

The implementation package was adapted at three district level hospitals but invariably the intervention maintained two core elements: the checklist and items on the checklist. Training sessions were led by the implementation lead and adapted to resources, available and interested personnel at each hospital as previously described.

Hospital 4 was not yet ready for the intervention during the implementation phase at Hospitals 1–3. Requests to introduce the project and gain necessary approvals were unsuccessful. However, the research team was able to present the project to Hospital 4 with the intervention results and changes in quality of care observed at Hospital 2 one year later. Hospital 4 then added a 'Diarrhoea Alert' block checklist permanently printed on the bottom right corner of the inside page of the blue board for all patients. This adaptation reduced the size of the checklist and avoided disruption to the front nursing orders page.

II. Inner Setting

3.2.2. Leadership Engagement, tension for change, and relative priority

All hospital sites required engagement of the hospital Chief Executive Officer or another executive-level representative before implementing the project. However, Hospital 2 leadership, executive leaders and front-line consultants (attending physicians), more widely communicated their support, increasing the tension for change and CDI intervention's priority. For example, influential senior consultant physicians invited the intervention for presentation at the weekly department of medicine meeting including consultants and physician trainees. Pre-implementation, the research team gathered feedback for adaptation, and then post-implementation presented the results at these department meetings.

Overall, the epidemiology and outcome results proved current quality of care was an intolerable status quo, with mortality at 30% and treatment inconsistent with global guidelines or not provided at all.[18] At the time of implementation, these epidemiology results were not yet published. Understandably, healthcare providers perceived TB and HIV as higher priority infectious diseases; South Africa has the greatest number of people living with HIV in the world and TB is a leading cause of death in people with HIV.[55,56] Nevertheless, Hospital 2 recognized the potential for the intervention to facilitate needed change and improve quality of care with evidence-based interventions. Key opinion leaders at Hospital 1 did not perceive the need for change; some providers did not see CDI as a problem.

III. Implementation Process

3.2.3. Engaging & Reflecting and Evaluating

3.2.3.1. Engaging: stakeholders. Overall, the research team engaged stakeholders, opinion leaders, peers, and experts similarly across the included hospitals as described in the methods, Table 1, and the *Leadership Engagement* construct in the Inner Setting domain (Table 3). Healthcare providers who were to use the new checklist were also engaged in the project with interviews and focus group discussions before and after implementation as described in the methods. Front-line provider stakeholders were engaged with the CDI education and intervention training sessions. These sessions included a socially engaging component with the distribution of "CDI Trained" buttons/badges to staff who completed the sessions. The buttons served to remind staff of the intervention, engaging those who may have missed the training, and create a community around the implementation process. The number of providers who became strong project champions varied substantially between sites.

3.2.3.2. Engaging: opinion leaders and champions. Support from opinion leaders for the intervention was a major distinguishing construct between hospitals. Some of these opinion leaders were also champions for

the intervention. Initial contact with opinion leaders was made by the external project lead except when one of those opinion leaders introduced the project to their senior administrators (e.g. the head of a department contacting a hospital administrator).

Project implementation leads were appointed for the project based on available resources and interest (external lead at Hospital 1, registrar and student at Hospital 2, pharmacy intern at Hospital 3). At Hospital 2, one of the project leads was an opinion-leading registrar. The registrar was a respected peer physician role model and informal leader; his opinion was valued by both senior and junior staff across the hospital. Together with the Department of Internal Medicine opinion leaders, the project leads were able to increase uptake at Hospital 2.

At Hospitals 1–3, nurse managers and administrators, including IPC and nurse educators, were engaged in the project. They accepted the project, recognized the need for the intervention, and affirmed its potential; however, they did not champion the project. Similarly, IPC nurses and nurse educators were engaged and supported the project but did not have as much influence as the consultant physicians. However, training sessions were introduced by the senior nurse administrators, nurse educators, and/or IPC nurses. These introductions were instrumental for building trust with the frontline staff. The training sessions were essential for creating awareness about CDI and its complications, as many of the nurses had limited awareness/knowledge preceding the sessions.[17] While nurses supported the intervention, they did not take ownership or see the intervention as part of their daily tasks. Nurses across the hospitals did not advocate for the intervention at the level the physicians championed at Hospital 2.

Furthermore, departments peripheral to internal medicine, such as surgery and emergency medicine, were also engaged and provided support for the intervention at both Hospital 1 and Hospital 2. Emergency medicine physicians were more supportive at Hospital 2 than Hospital 1. While Hospital 1 leaders were supportive, they did not have the same level of influence that consultants at Hospital 2's Department of Medicine had on other providers. The Hospital 2 consultants were then able to facilitate successful recruitment of staff, nurses, and junior physicians to participate in the intervention. As a result, the strong opinion leaders, including the senior level physicians, who championed the intervention at Hospital 2 were able to overcome indifference toward the intervention.

3.2.3.3. Reflecting and Evaluating. Preliminary assessment of progress and impact of the implementation pilot included the quantitative data from patients with CDI test results, observations, and qualitative interview data. Despite perceived challenges and low use at Hospital 1, the increase in CDI testing and awareness observed in post interviews indicates that there was an increase in CDI knowledge due to the implementation package. The centralization of printing checklists for Hospitals 1 and 2 suggests that the implementation package initiated became a sustained change in organizational structure.

Comparison of our baseline data from four area hospitals (including Hospital 2) and Hospital 2 baseline results alone to post-implementation results signal improvements in CDI management and patient outcomes (**Appendix**: Reflecting and Evaluating). The results were not statistically significant nor was the study designed to detect statistically significant differences due to the short follow-up period. Measurable progress in improving quality of care and implementation uptake was greatest at Hospital 2.

Overall, the implementation of the intervention was associated with a self-reported heightened awareness and increased use of evidence-based CDI practices at the participating South African hospitals. Furthermore, the intervention demonstrates the capacity and potential of the "Diarrhoea Alert" to improve the quality of CDI care in South Africa when appropriate champions are engaged in the implementation effort.

4. Discussion

This study achieved its objective of developing a context specific intervention for CDI and identified key constructs for intervention uptake in South African public sector district level hospitals. This study identified key implementation science constructs that uniquely distinguish high intervention uptake at one hospital compared to two other South African district level hospitals with similar available resources and organizational structure. The new FRAME-IS is regarded as the first framework to be specific to implementation strategy modifications; we provide one of its first applications.[36] The FRAME-IS documented how the most relevant ERIC implementation strategy utilized, 'Identify and prepare champions,' was adapted to fit the interest and available personnel at each site with a co-creation approach. These changes in personnel leading the intervention were made proactively, prior to implementation, and related CFIR constructs emerged as highly relevant to the intervention's success.

First, tension for change was one of the most relevant constructs to distinguish uptake between the hospitals. The tension for change and prioritization communicated from leadership at Hospital 2 supported high intervention uptake. An academic partnership with the tertiary hospital, specifically the AMS ward rounds (Structural Characteristics), uniquely supported this tension for change at Hospital 2. Second, the individuals who championed the intervention at the hospital with a greater tension for change uniquely supported the intervention and contributed to its success. A position of influence and investment appeared to be a required characteristic of the champions to support intervention uptake. Additional CFIR constructs that proved to be highly relevant were intervention complexity and stakeholder engagement. The results imply strategies to engage low resource hospital settings without strong academic partnerships must adapt. The relevance of this work is that it unveils unique and universal challenges in South Africa that can be considered for how this applies to other low resource settings. Ultimately this study strives to promote the use of evidence-based practices for identifying, treating, and preventing CDI in low resource settings, and adds to the growing application of implementation science theories and frameworks in LMICs.

Implications from this research can be applied to pharmacy-led and interprofessional interventions in low-resource settings. A recurring theme in South Africa was the importance not only of champions' influence or seniority but also their level of investment in the project. For example, at Hospital 2, the senior registrar (i.e. resident) and medical intern who championed the project had strong investment and the support of seniority to influence uptake. In contrast, the pharmacy intern at Hospital 3 was highly invested in the project but lacked seniority to influence uptake and spread change. Culture within professions and hierarchy among groups contribute to the challenges of interprofessional teamwork; meanwhile interprofessional communication is essential for patient safety.[57,58] Broadly, South Africa can be categorized as having a moderate power distance where hierarchy is accepted and followed.[59] Healthcare providers lower in the social hierarchy may not speak up to issues they perceive, threatening patient safety.[58,60] The results of this study, specifically the key differences in uptake associated with the profession leading the intervention, is consistent with prior work in South Africa that a healthcare hierarchy seems predominant and negatively affects interprofessional communication.[61] These cultural factors in South Africa may have also influenced the observed reluctance from nursing staff to take ownership of the intervention across the three hospitals. Thus, there is a crucial need to address inner setting factors such as readiness for change and psychological safety to support interprofessional interventions in the context of low resource settings.[28,62–65] Pharmacy-led interventions must also be mindful of forming interprofessional teams that are informed by the institutional culture and socio-political context.

Strong academic partnerships and a culture of supporting new initiatives also distinguish Hospital 2 from the hospitals with low uptake.

Broadly, community academic partnerships are described in implementation science research as a critical component to implementing evidence-based practices and a cornerstone of many academic programs[66] To various extents, this project utilized recognized strategies, specifically: identifying barriers and facilitators to implementation, facilitating interactive problem solving, tailoring strategies, promoting adaptability, and auditing and providing feedback during the implementation phase. While the research team engaged healthcare stakeholders throughout this research, a community advisory board, a strategy not deployed, could strengthen this intervention, uptake, and systematic evaluation of these strategies.[66]

Finally, the straight-forward CDI intervention enabled its success at Hospital 2, and it could support sustained and scaled intervention. Simple interventions are more likely to be effective, and thus evermore crucial in overburdened public hospitals.[67,68] The checklist can now be printed for the Western Cape hospitals on 'tender', a centralized procurement process all government facilities follow.[69] The checklist can operate without intervention from the research team, should healthcare personnel continue to use the checklist and the administration sets this expectation. The adaptation of the checklist being printing directly onto the prescription chart Hospital 4 is a sustainable and scalable iteration. Training, monitoring and providing feedback on the checklist's use could be provided through mechanisms for IPC monitoring already in place as well as be included in IPC training already routinely provided. Scalability is likely because the personnel, physical structure, and resources available within district level hospitals are very similar across the Western Cape. However, micro- and socio-cultural differences exist within each hospital, such as those that emerged in this study. Across South Africa, variations may exist in provincial level priorities, administrative structure, and funding. The National Department of Health could scale intervention dissemination in the Western Cape and across South Africa. Adaptation is likely needed to fit province level differences in supplies, such as the prescription chart and order forms. Globally, the intervention may also be relevant to other governmental health systems. A fidelity assessment of both the sticker and the embedded prescription chart checklist form is needed to guide continued improvement.

4.1. Limitations

This study is a relatively small-scale study in a broadly understudied setting. Time to develop the implementation package, implement, and collect post-implementation results was also short. However, the research identified compelling themes between the hospitals. The results may be generalizable to healthcare settings outside of the Western Cape, South Africa with similar resources, challenges, and education systems. Researchers have adapted and applied the CFIR framework with and without numeric valence ratings assigned to constructs, both prospectively and retrospectively.[31,70,71] Earlier integration of the CFIR framework in this research could have strengthened the analysis and is recommended.[31,71] For example, our a-priori semi-structured interview guide was not structured to collect sufficient details for individual level analysis. This is an area for future research. Yet, we were able to detail facilitators and barriers to CDI care in a prior qualitative study, and apply the implementation science principles described in the methods.[17] A limitation of the analysis is that the CFIR dimensions are not quantified, but nevertheless they identify the constructs that are strongly associated with uptake through a process of author consensus. Additionally, such investigator bias, including those leading the project and key collaborators from South Africa and the United States cannot be extracted. To reduce this bias, qualitative interview data was coded by two additional researchers less directly invested in the study results. Some authors were involved in all or select phases of the intervention development, implementation, data analysis, and reflective analysis. The CFIR conceptual framework also aided in structuring a systematic evaluation of the intervention and implementation. Accordingly, this participatory approach is both a strength of the research process and a limitation of the results.

5. Conclusions

This study provides a health systems strengthening intervention for CDI that is both needed and uncomplicated, in an understudied LMIC setting, and an analysis of the intervention uptake with the CFIR and FRAME-IS frameworks. This research provides a breakdown of the intervention development, implementation, and outcomes at three district level hospitals in Cape Town, South Africa. The results show uptake was highest in the hospital with tension for change, influential champions, and existing academic partnerships. The FRAME-IS precisely highlights how proactive collaborative implementation adaptations supported intervention uptake. In understudied settings with fewer academic connections, implementation researchers should first assess readiness for change and then test implementation strategies that could support collaborative intervention and implementation development.

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CRediT author statement

Laurel Legenza: Conceptualization, Project administration, Methodology, Investigation, Formal analysis, Data Curation, Writing - Original Draft, Writing - Review & Editing. Renier Coetzee: Conceptualization, Project administration, Methodology, Formal analysis, Writing - Review & Editing, Supervision. Warren E. Rose: Conceptualization, Methodology, Writing - Review & Editing, Supervision. Tasneem Esack: Formal analysis, Writing - Review & Editing. Kenneth Crombie: Investigation, Formal analysis, Writing - Review & Editing. Megan Mina: Investigation, Formal analysis, Writing - Review & Editing. Nasia Safdar: Conceptualization, Methodology, Writing - Review & Editing, Supervision. Susanne G. Barnett: Conceptualization, Methodology, Writing - Review & Editing, Supervision.

Declaration of interest

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Appendix. Supplementary data

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Appendix M: ***Research in Social and Administrative Pharmacy*** **author guidelines**

RESEARCH IN SOCIAL AND ADMINISTRATIVE PHARMACY

AUTHOR INFORMATION PACK

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Appendix N: Supplementary results file from *Research in Social and Administrative Pharmacy* publication

Appendix N

Strengthening South African district hospitals with the implementation of a *Clostridioides difficile* infection intervention: understandings from the Consolidated Framework for Implementation Research (CFIR)

Checklist Training and Adaptations &

Moderately relevant CFIR constructs and additional detail on highly relevant constructs

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I. Checklist Training and Adaptations

For the education sessions, the training nurse introduced the lead researcher to the nurses in the wards. The lead researcher provided checklists to the ward and conducted a trial of the intervention and implementation with the nurses in one of the internal medicine wards at Hospital 1. The trial included applying the checklist sticker to medical charts of patients with diarrhoea, conducting education and training sessions, and daily follow-up by the lead researcher on the checklist use and understanding of the intervention. Physicians were concurrently trained as available during the weeks of nurse training and follow-up. Poster reminders for the intervention were also created to fit the setting. The lessons learned from the education and trial implementation were utilized to adapt the implementation expansion to the remaining wards, the pharmacy, and the emergency department in Hospital 1.

Training times were adapted to meet the availability of all available healthcare providers in the medical wards, surgical wards, and the emergency department. This included scheduling around other staff development events already scheduled during the preferred training time for some nurses. Training occurred over two-week periods that included two training sessions on each ward to cover the shifts of providers that work alternate days. The first week aimed to reach all available providers, while the second week provided training to anyone who missed sessions the previous week and follow-up to those already trained. The lessons learned from the implementation in Hospital 1 were utilized to adapt the implementation to Hospital 2, namely the inclusion of local peer champions who were supported by Hospital 2's Department of Internal Medicine.

II. Intervention/Innovation

A. *Complexity – Highly relevant (additional details here)*

The intervention was regarded as 'quite simple.' The checklist avoided altering standard work processes, and instead simply triggered reminders to identify patients with diarrhoea, provide quality of care measures, test patients at risk for CDI, treat patients with CDI, and apply IPC procedures (Figure 2). In addition to treatment, the other quality of care measures triggered were rehydration, discontinuing unnecessary antibiotics, and stopping loperamide. Loperamide is contraindicated in patients with CDI.[1,2] The most complex step was the physical application of the checklist sticker to the blue boards of all patients with diarrhoea, because despite our design of including all providers, it was mostly the physicians who applied the stickers. Our instructions were that any health care provider could apply the alert similar to the culture of safety interventions where anyone can alert a rapid response team. Evidence-based patient safety interventions include alerts that anyone can raise, such as to a rapid response team.[3]

Furthermore, the checklist prompted the use of existing resources and steps available, for example contact precautions and laboratory tests. No specialized tasks were added. Meanwhile, our baseline study found the quality of care measures such as oral rehydration and contact precautions for CDI patients, were not often practiced. The checklist served as a reminder for treatment options that are available but are often delayed or not initiated at all. The intervention was designed as a reminder of key quality of care measures and CDI-related tasks ultimately to be cost- and life- saving by reducing CDI-associated length of stay and mortality. Furthermore, treatment that was inconsistent with national and international treatment

guidelines was improved by the checklist, which organized and prompted these quality of care measures for patients with diarrhoea and CDI risk factors.

B. *Source – Highly relevant (additional details here)*

The innovation area was selected by internal South African leaders and local healthcare providers via a participatory process. We selected AMS as the topic area through this stakeholder engagement, including visits with Department of Health administrators. Furthermore, with a SWOT analysis of AMS projects and innovation areas, CDI was selected due to the lack of known data at the district level in the Western Cape province.

C. *Evidence Strength and Quality – Moderately relevant*

Strong high-quality evidence for checklists in healthcare and checklist bundle interventions exist.[4-6] Checklists are an evidence-based intervention shown to increase quality of care for CDI among other infections.[7-9] Awareness and perceptions of these CDI interventions and other bundle approaches varied among healthcare providers: for example, providers with experience working in high-resource settings outside of South Africa, such as the UK, were more aware of CDI. These providers told anecdotal stories of heightened IPC practices for CDI not observed in South Africa. Other providers believed a CDI innovation could provide initial benefit and was a worthy endeavor; however, they doubted changes would be sustainable. At the time that we developed the checklist, our epidemiology results showed a high CDI-associated mortality rate and opportunities for improving quality of care.[2]

III. Inner Setting

A. *Structural Characteristics – Moderately relevant*

The social structure of the district hospitals included is similar to other public district level hospitals across Africa and other low resource healthcare settings. Various levels of nurses provide care to patients on open format hospital wards under the supervision of nursing managers. A few consultant physicians supervise many registrars, interns, and students. The pharmacy provides primarily dispensing services with limited-to-no clinical services. However, the pharmacy profession is growing in South Africa, and pharmacists are starting to participate in ward rounds, most commonly at Hospital 2. A weekly AMS ward round also occurs at Hospital 2 and includes pharmacy and medicine presence along with trainees. The AMS ward round is often led by an infectious diseases expert from the tertiary teaching hospital/university.

B. *Networks and Communication – Moderately relevant*

The Department of Internal Medicine at Hospital 2 uniquely had a WhatsApp communication system for laboratory results, patient needs, and program reminders, including reminders about the CDI intervention.

C. *Available Resources - Moderately relevant*

Time and the personnel involved with the project were resources that varied for the implementation at each hospital. Tangible resources available, such as medications, IPC supplies (gloves, gowns, soap etc.), and other supplies were similar at all publicly funded district hospitals. Existing IPC programs demonstrated the capacity for hospitals to provide IPC measures and the necessary supplies were usually available, while contact precautions were not commonly ordered for patients with CDI in the baseline study. Nurses cited a shortage of time, attributed to staffing shortages, as a major barrier to performing IPC measures.

Project leads had unique responsibilities that affected their time available for project activities. The lead researcher serving as the project lead at Hospital 1 had the most dedicated time to the implementation. Additional project leads at Hospital 2, a registrar and medical intern, could perform the follow-up training and reminders during regular daily ward rounds. Meanwhile, the project lead at Hospital 3, a pharmacy intern, had the least amount of time dedicated to the intervention, as primary responsibilities were located away from the hospital ward in the pharmacy and she had less time to go to the ward to follow-up on the project and perform follow-up engagements.

D. *Access to Knowledge and Information - Moderately relevant*

The barriers and facilitators study identified limited CDI knowledge as a major barrier to CDI treatment. Some providers had not learned of CDI before and were unsure of how to diagnose, treat, and prevent CDI transmission. The implementation process included CDI education and training materials in a digestible format. These materials, handouts, and the in-person training sessions on the ward or other convenient locations were similar across sites. The implementation also included reminder posters of intervention steps posted in the wards (when to apply the checklist, the checklist example, directions on where to find the checklist, and contact information to ask questions).

III. Implementation Process

A. *Reflecting and Evaluating – Highly relevant (additional details here)*

Preliminary assessment of progress and impact of the implementation pilot included the quantitative data from patients with CDI test results, observations, and qualitative interview data. Despite perceived challenges and low use at Hospital 1, the increase in CDI testing and awareness observed in post interviews indicates that there was an increase in CDI knowledge due to the implementation package.

The centralization of printing checklists for Hospitals 1 and 2 suggests that the implementation package initiated became a sustained change in organizational structure. The local healthcare providers requested centralized printing from the Department of Health which ensures a sustained stock can be maintained without renewal authorizations. The intervention and implementation at Hospital 4 was augmented through the addition of the checklist items as a diarrhoea alert in all drug order forms. This represents perhaps the most sustainable adaptation and health system change.

Comparison of our baseline data (retrospective review of 112 patients with a C. difficile positive result) from four area hospitals (including Hospital 2) and Hospital 2 baseline

results alone to post-intervention results demonstrates numerical improvements in CDI management.[10] Measurable progress in improving quality of care and implementation uptake was greatest at Hospital 2. However, the results were not statistically significant nor was the study designed to detect statistical differences due to the short follow-up period. Uptake and the number of positive results of Hospitals 1 and 3 was insufficient for analysis.

Nevertheless, at Hospital 2 seven patients had a positive *C. difficile* test result during the 90-day evaluation period and six of those patients had the checklist in their medical record. Compared to multicenter baseline data, orders for oral rehydration increased from 12% to 43% and orders for contact precautions increased from 36% to 86%. Continuation of loperamide during CDI treatment decreased from 41% to 14%. Patients not receiving antibiotic treatment for CDI decreased from 29% to 14%. One patient died (14%) in-hospital (30-day in-hospital baseline mortality 29%).

The lead researcher presented results at each hospital in person via formal individual and group discussions and presentations. A team debriefing about progress, experience, and results was conducted with project leads and opinion leaders, including executive administrators at Hospitals 1-3. At Hospital 1, a formal presentation of results was presented to physicians during their monthly education session. Similarly, at Hospital 2, results were presented to physicians during their education sessions. Results from Hospital 2 were also presented to the Department of Health and Hospital 4 during an invited presentation to hospital leadership. Results at Hospital 3 were presented to the Western Cape Department of Health as part of the internship program.

Feedback on the intervention was positive. A salient recommendation was to reduce the size of the checklist to take up less space on the prescription chart and not block other areas of the chart. This was accomplished with Hospital 4's adaptation. Centralization of the intervention with concurrent activities, such as other IPC nurse education activities such as hand hygiene, and TB (e.g. mask use) awareness, and skills trainings was suggested by front line key informants, including nurses, and are likely to be more effective.

Overall, the implementation of the intervention led to a heightened awareness and increased use of evidence-based CDI practices in South Africa. Furthermore, the intervention demonstrates the capacity and potential of the "Diarrhoea Alert" to improve the quality of CDI care in South Africa when appropriate champions are engaged in the implementation effort.

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Appendix O: ***Journal of The Pharmacy Society of Wisconsin*** **epidemics publication**

Appendix O

PHARMACIST CE:

The Pharmacists Role in Combating Statewide Epidemics

by Cody J Wenthur, PharmD, PhD, Laurel Legenza, PharmD, MS, Nicole Weinfurter, 2019 PharmD Candidate, Ashley Lorenzen, PharmD, BCPS, Dean Bowen, 2020 PharmD Candidate

CE FOR **PHARMACISTS**

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Learning Objectives

- Summarize the CDC's definition of an epidemic
- Describe the impact of the opioid, *Clostridium difficile* infection (CDI), and obesity epidemic in Wisconsin and the United States
- Identify tools and education pearls to provide patients related to epidemics affecting Wisconsin residents
- Recommend evidence-based treatments to help combat each the opioid, *Clostridium difficile* infection (CDI), and obesity epidemic.

The word "epidemic" carries a lot of weight. It is a word that can instill fear and a sense of urgency in a population. It ultimately means there is a serious issue that is negatively affecting a high proportion of that population and needs to be addressed immediately. The Centers for Disease Control and Prevention (CDC) defines an epidemic as, "an increase, often sudden, in the number of cases of a disease above what is normally expected in that population in that area."[1] The CDC has also quantified an "epidemic threshold" for pneumonia and influenza deaths that could be applied to other healthcare issues.[2] The "epidemic threshold" is met when there is an increase of 1.645 standard deviations above the seasonal baseline of pneumonia and influenza deaths.[2]

The United States (US) has dealt with various epidemics in the past. Examples of diseases causing epidemics which have been eradicated include polio, with the last case in the US occurring in 1978, and smallpox, which was eradicated from North America in 1952.[3,4] Currently in Wisconsin and the US, there are a number of epidemics affecting vast amounts of people. Three examples were pharmacists have the opportunity to get involved and assist with epidemic mitigation include opioid misuse, *Clostridium difficile* (*C. diff*), and obesity. Pharmacists are very accessible healthcare providers and may see patients up to a monthly basis. Pharmacists can recommend optimal antibiotic and pain management therapy, educate patients on how to use their medications properly, and provide diet and lifestyle interventions. The objective of this article is to describe the scope of each epidemic, how pharmacists can play a role in mitigating the epidemic, and present tools that pharmacists can recommend or use.

Background and Epidemiology of the Opioid Misuse Epidemic

Balancing the risks and benefits of opiate receptor agonists as analgesics has been a challenge in pain management for thousands of years, beginning with the use of products derived from the opium poppy, papaver somniferum.[5] As modern medicine promoted the increased availability and rapid expansion of semi-synthetic opioids, the need for proper management of this risk-benefit profile has likewise expanded to cover hundreds of millions of acute and chronic pain patients worldwide.[6] This growth has been especially dramatic in the US.[7,8] Opioid prescribing rates in the US peaked in 2012, with a rate of 81.3 prescriptions written for every 100 individuals. Although rates have recently declined, Wisconsin remains above the national average with 62.2 opioid prescriptions written per 100

individuals.[9] Although the expansion of access to appropriate pain control is a desirable public health outcome overall, the specific increase in opioid pain reliever utilization as a means to this end has unfortunately been a major driving force in the continuation of a general drug overdose epidemic and resurgence of broader opioid misuse.[10,11] Indeed, the magnitude of the problem has increased to the point where the US Department of Health and Human Services declared the opioid crisis to be a public health emergency.[12] In 2016, there were about 63,600 deaths nationwide due to drug overdose – a more than four-fold increase since 1999.[13] Within Wisconsin, there were approximately 20,600 individuals diagnosed with opioid use disorder (OUD) and 827 deaths due to opioid-associated overdose in 2016.[14] This corresponds to a rate of approximately 20 opioid overdose deaths per 100,000 people; drug overdose accounted for 15.5% percent of deaths amongst individuals 18-25 and 7.1% of deaths in 26-64 year old individuals in 2015.[15]

In response to the opioid crisis, the US government issued the Comprehensive Addiction and Recovery Act (CARA) in 2016, which was the first major legislation to address substance use disorder in over forty years.[16] This act contained measures to respond to the opioid overdose crisis across six distinct areas: law enforcement, criminal justice reform, prevention, treatment, recovery, and overdose reversal. The Heroin, Opiate, Prevention and Education (HOPE) agenda was instituted in Wisconsin in 2013 to address many of these same concerns, and expansion on this agenda through a dedicated task force and special legislative session has resulted in 28 enacted pieces of legislation to date.[17] Several of these laws directly impact the daily practice of pharmacy in the state, including a requirement to view and record identifying information from patients picking up a schedule II or III drug, a requirement to have a prescription for codeine cough syrup, and implementation of a statewide standing order for naloxone pharmacist dispensing.[18-21] Other laws have an indirect impact on pharmacist counselling and referral strategies, such as those expanding good Samaritan coverage and legal protections for individuals reporting or experiencing opioid overdose, and those funding additional medically assisted treatment (MAT) centers in underserved areas.[22-24]

TABLE 1. Risk Factors for Opioid Overdose

Medication-Related Factors	*Patient-Related Factors*
Combining opioids and benzodiazepines	Age ≥ 65 years
Daily dose ≥ 100 morphine mg equivalents	Sleep-disordered breathing
Long-acting or extended release opioid formulation	Renal or hepatic impairment
Long term opioid use for ≥ 3 months	Major depressive disorder
≤ 2 weeks since initiating long-acting opioid formulation	Substance use disorder
	History of drug overdose

Role of Pharmacists in Reversing the Opioid Misuse Epidemic

As the primary point of care for medication therapy expertise, pharmacists are optimally positioned to take advantage of these tools and help end the opioid misuse epidemic. At a broad level, the CDC identify a four-fold role for pharmacists in vigilance for signs of opioid misuse: assessment, verification, consultation, and communication.[25] Assessment is focused on identifying red flags associated with misuse, such as forged or altered prescriptions and inconsistent or early refills. Verification is used to validate proper therapeutic use, check prescriptive authority through the Drug Enforcement Administration (DEA), and confirm proper patient identification. Consultation with available patient records and prescribing databases is then recommended to identify possible misuse. Finally, communication with the patient and prescriber and submission of relevant information to the written record should be incorporated in order to allow for ongoing monitoring and risk-assessment by all parties.

However, individual pharmacists are ultimately responsible for applying these general vigilance roles in a way that leads to meaningful improvements in patient outcomes. Fortunately, multiple tools are available to support both preemptive opioid misuse risk reduction and interventional harm mitigation, while still preserving compassionate therapeutic care. Pharmacist-driven resolution of the opioid misuse epidemic would take maximum advantage of these tools by concurrently addressing multiple areas of need, including consistent risk and harm screening, expanded public education on proper opioid use, ongoing promotion of best-practice opioid prescribing, effective support for medication-assisted recovery from opioid use disorder, and reliable dispensing of pharmacological protection against fatal opioid overdose.[26]

Reducing Likelihood of Opioid Misuse in At-risk Patients

Although open-ended, empathetic, and non-judgmental questioning regarding opioid medication use is often an appropriate and sufficient method to perform a simple assessment for patient risk of misuse, there are also a number of risk screening tools available when formal metrics are desired.[27,28] These include the opioid risk tool (ORT), screener and opioid assessment for patients with pain (SOAPP), diagnosis, intractability, risk, efficacy score (DIRE), the brief risk interview (BRI), brief risk questionnaire (BRQ), and screening instrument for substance abuse potential (SISAP). Although the SOAPP tool is among the most well validated, there is little evidence of superior performance between any of these screening measures, so selection of the appropriate tool is contingent upon considerations such as prior experience and ease of access.[29] Specific assessment of patients for elevated

TABLE 2. Treatment Options for Opioid Withdrawal Symptoms

Withdrawal Symptoms	*Common Treatment Choices*
Autonomic Hyperactivity	clonidine, tizanidine, lofexidine
Muscle Cramps / Pain	ibuprofen, ketorolac tromethamine
Diarrhea	bismuth subsalicylate
Nausea / Vomiting	prochlorperazine, ondansetron
Insomnia	Non-pharmacologic treatments preferred

risk of overdose can be undertaken by providing patients with a self-screening checklist generated by the Wisconsin Department of Health Services.[30] This document allows pharmacists to identify common medication- and patient-related risk factors (Table 1), providing a platform to initiate discussion of how to safely and correctly use opioid medications in the event that such risk factors are identified.

Published guidelines on opioid prescribing are effective tools for verification and implementation of proper therapeutic use.[31] The predominant, current guidelines at the national and local levels are the CDC Guideline for Prescribing Opioids for Chronic Pain and the Wisconsin Medical Examining Board Opioid Prescribing Guidelines.[32,33] Overall, these guidelines espouse four key principles for safe opioid prescribing for the treatment of adults with non-cancer pain: identify and treat the cause of pain, use non-opioid therapies when possible, start with a low dose and increase dosage slowly, and provide close follow-up. Adherence to these key principles should be considered for every opioid prescription that is processed. Additional recommendations from the Wisconsin guidelines include the use of short-acting opioids for initial dose titration, avoiding oxycodone as a first-line therapy, discouraging methadone prescribing by inexperienced or inexpert practitioners, and writing new prescriptions for treatment of acute pain to less than three days in most cases. Pharmacists should communicate with prescribers to clarify and correct when deviations from these recommendations are identified, remembering that the desired outcome is to support safe use of opioids overall, rather than to simply limit access.[34]

Consultation of the enhanced Wisconsin Prescription Drug Monitoring Program (ePMDP) will now identify more cases of potential opioid misuse due to an administrative rule change allowing e-prescribing for Schedule II controlled substances and recent legislation mandating practitioner review upon initial prescription of a schedule II drug.[35-36] This law resulted in dramatically increased overall use of the ePDMP in 2017, although pharmacist use remained relatively steady at round 70,000 queries per month.[37] The same legislation also decreased the time requirement for submission of dispensing information from 7 days to 24 hours, to make the database more timely and accurate. In addition to multiple prescriber and/or dispenser alerts, the ePDMP also provides safety alerts regarding specific actionable scenarios that increase risk of overdose, such as concurrent opioid and benzodiazepine overlap.[38]

In terms of risk communication, the provision of proper storage and disposal instructions to patients using opioids remains an important pharmacist task. The majority of misused prescription medications are given by, bought from, or taken from a friend or relative.[39] Therefore, pharmacists should continue to counsel patients to store opioids in a secure, preferably locked, location, and offer self-disposal instructions for opioids. These options include trashing them with coffee grounds or kitty litter, or flushing unused medications down the toilet, as many opioids are on the approved Food and Drug Administration (FDA) flush list.[40] Furthermore, the increasing availability of community resources for returning or destroying unused or unwanted opioid medications should also be emphasized. These resources include a growing network of drug takeback locations such as local police or fire stations, expansion of mail-back programs, and periodic statewide drug take-back days.

Mitigating Harms for Patients with Opioid Use Disorder (OUD)

While the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is the prevailing standard for providers to identify OUD, there are also several screening tools available for pharmacists to quickly identify concerning opioid misuse patterns in the absence of information regarding a formal OUD diagnosis.[41] These include the current opioid misuse measure (COMM), the drug abuse screening tool-20 (DAST-20), and the National Institute on Drug Abuse-modified Alcohol, Smoking, and Substance Involvement Screening Test (NM-ASSIST) screen.[28,29] Although more evidence is needed to determine their validity in pharmacy settings, these tools can still support preliminary stratification of patients with, lower, moderate, or high risk opioid misuse, providing the opportunity to advise on proper medication use, assess patient readiness to change, offer assistance with the process of changing, and arranging a referral for specialty OUD assessment and treatment, if necessary.

Amongst patients diagnosed with OUD, pharmacists have a direct role in the management of current opioid therapy, including initiation of a dose taper regimen and associated withdrawal symptom support. The recommended rate of taper in patients experiencing harms from opioid use is a 25% reduction in morphine milligram equivalents (MME) per week, although this range can vary between 2 – 50%, depending on setting and patient needs.[33,42] If patients need pharmacologic support for autonomically-mediated withdrawal symptoms such as lacrimation, rhinorrhea, sweating, chills, hypertension, tachycardia, or mydriasis during this taper, pharmacists can recommend use of an appropriate agent, such as oral clonidine or tizanidine.[33] Ancillary symptoms

arising from withdrawal should be treated supportively as needed (Table 2).[43] Options for ongoing medication assisted treatment (MAT) should also be communicated to patients with OUD and their providers, including monthly naltrexone intramuscular injections, daily methadone oral tablets, and daily buprenorphine-containing sublingual preparations.[44] When selecting an appropriate MAT regimen, the potential for precipitation of withdrawal symptoms with naloxone and buprenorphine should be considered, as should the dose accumulation and elevated risk of overdose with methadone. Integration of appropriate non-opioid and non-pharmacologic pain control methods in individuals experiencing ongoing pain is also a crucial consideration for compassionate treatment of these patients.

Mitigating Harms in Cases of Opioid Overdose

Education of members of the public to recognize and respond to opioid overdose symptoms is an effective method by which mortality due to opioid misuse can be reduced.[45,46] Opioid overdose is characterized by respiratory depression, manifesting as slow, shallow, or absent breathing. An overdosing individual will be difficult to rouse, including by yelling or painful stimuli, such as a sternal knuckle rub. They may make snoring, gurgling, or choking noises while asleep or nodding off. Additionally, they may be vomiting, have blue or pale lips, skin, or fingernails, and the individual's face may appear pale or clammy. Incorporating a frank discussion of these symptoms alongside other potential adverse effects of opioid medication is recommended, especially in patients with risk factors that increase the likelihood of overdose. When overdose is suspected, individuals should call 911, open the airway and give one rescue breath every five seconds if the individual is not breathing and has a pulse, give naloxone if available, place the person on their side with the top leg and arm crossed over the body, and stay with the individual until help arrives, re-administering naloxone as directed.[47]

As a component of this response, administration of the opioid receptor antagonist naloxone is the most effective method to avoid a fatal opioid overdose, reversing 89% of cases where it is used.48 Pharmacists in Wisconsin may now dispense naloxone without a prescription pursuant to a statewide standing order. Consistent application of this authority by pharmacists has the potential to drastically alter the trajectory of the opioid misuse epidemic in the state and significantly reduce opioid overdose mortality, as one life can be saved for every 227 naloxone kits dispensed.[49] Unfortunately, the stigma associated with opioid use disorder currently results in very high rates of patient resistance to hear about or accept naloxone.[50,51] Therefore, in order to maximize the impact of this intervention, pharmacists need to be cognizant of this stigma and take steps to actively mitigate its impact. This includes avoiding terms like 'addict' during discussion and normalizing naloxone dispensing as a measure that is undertaken as a matter of course to maximize the benefits of opioid use while limiting its potential risks.

Specific naloxone products available for dispensing include intramuscular injections (manual or auto-injector) and intranasal sprays (single-step or multistep). The single-step nasal spray is a simple, widely-available, and easily-

transportable method suitable for use by most individuals who have received basic administration information. The auto-injector is a useful option where the individual administering the naloxone is likely to have limited experience or information about the situation and patient, as it provides audible step-by-step instructions for use; however, these instructions are only provided in English.[52] All naloxone containing products should be protected from light and prevented from undergoing extreme temperature fluctuations. Products with needles should be placed in a puncture-proof container upon use, and any unused or expired naloxone should be returned using a drug take-back program. Naloxone dispensing records under the statewide standing order need to be reported quarterly using prescriber number 1346552668, including the number of doses dispensed, number of refills dispensed, number of different dosage forms dispensed, and any challenges or barriers encountered.[20,21] Patient counselling on any of these naloxone products should cover overdose risk factors, overdose signs/symptoms, and overdose response measures, along with administration, storage, and disposal instructions. If the individual being counseled on naloxone rescue is also the one taking an opioid medication, they should be instructed to communicate this naloxone use information with a caregiver or other responsible individual, as the patient would likely be unresponsive or too confused to take action themselves in the event of an overdose.

Summary Statement

The tragic impact of the opioid misuse epidemic continues to be felt throughout the country and within the state of Wisconsin, especially through fatal opioid overdose. However, recent legislative changes have provided pharmacists with direct access to life-saving pharmacological tools to address this problem, as well as improved screening measures to recognize and correct misuse. Furthermore, specific guidelines are available to optimize opioid therapy at a population level, and access to MAT options for patients with OUD continues to expand. By employing these tools, pharmacists have the opportunity to build upon recent gains in this high-need area, directly saving patient lives across the state of Wisconsin.

Background on *Clostridium difficile*

Clostridium difficile is the most common pathogen causing healthcare-associated infections.[53] *C. difficile* is a spore forming bacteria that can cause diarrheal infections ranging from mild-moderate to life threating colitis and sepsis. Patients will usually present with diarrhea and abdominal cramps and other signs of infection including, increased white blood cell count; CDI is diagnosis by a stool test.

At the turn of the century *C. difficile* infection (CDI) caused massive outbreaks in hospitals across North America and Canada that were associated with highly virulent *C. difficile* strains.[54] Since then CDI bundle approaches for appropriate prevention, treatment and diagnosis, along with antibiotic stewardship programs have halted what was a rapid increase in infection rates.[55,56] Nonetheless, the CDC continues to classify CDI as an urgent threat. CDI is also occurring without recent healthcare exposure or as community onset CDI, in recently discharged patients, and in long-term care facilities.[57]

Epidemiology of *Clostridium difficile*

According to the CDC *C. difficile* is associated with 453,000 infections per year and about 15,000 of these infections result in death directly attributable to CDI.[58] *C. difficile*, transmitted via a fecal oral route, can be toxigenic or non-toxigenic. Non-toxigenic strains can colonize the gut of individuals without infection. The toxigenic form can lead to active infection, especially in the setting of antibiotic use that kills normal gut flora, but not *C. difficile*, allowing it to overgrow. The toxins cause intestinal enterocytes to loose integrity and subsequently cause an inflammatory response, associated with the severity of the infection.[59] CDI incidence and severity increased rapidly, including fatal outbreaks in the early 2000s. These outbreaks were associated with the hypervirulent *C. difficile* BI/NAP/027 strain. However, a recent CDI epidemiology study conducted across Veterans Affairs Medical Centers (2011-2016) found a decrease in the overall BI/NAP/027 strain prevalence from a high of 26.2% in 2013 to 16.9% in 2016.[56] The recently revised Infectious Diseases Society of America (IDSA) guideline classifies CDI by severity and setting/timing of onset, including healthcare associated (healthcare facility onset [>3 days after admission] or community-onset/healthcare associated [within 12 weeks of healthcare facility discharge]) and community associated.[60]

Antibiotic exposure is the most critical and modifiable CDI risk factor. Antibiotics associated with high CDI risk are those that are broad spectrum and affect normal gastrointestinal flora. A meta analysis of antibiotic classes and community-associated CDI risk found clindamycin, fluoroquinolones, and a combined group of cephalosporins, monobactams, and carbapenems had a high CDI risk. Macrolides, sulfonamides-trimethoprim, and penicillins had a lower CDI risk. Tetracycline had no association with CDI in this study.[61] Prolonged antibiotic durations and multiple antibiotics also increase risk. In a study of cumulative antibiotic exposure patients who received 1st-2nd generation cephalosporins (HR 2.4), 3rd-4th generation cephalosporins (HR 3.1), quinolones (HR 4.5), and sulfa drugs (HR 1.8), intravenous vancomycin (HR 2.6) were more likely to develop CDI relative to patients who did not receive these antibiotics, independent of other antibiotics received. The minimal gastrointestinal exposure from intravenous vancomycin exposure is thought to disrupt normal flora enough for *C. difficile* to overgrow without killing it. Patients who received two antibiotics had a 2.5-fold increase in risk compared to those who received one antibiotic.[63] The increased risk of CDI persists during antibiotic therapy and three months following therapy discontinuation. Even a prophylactic single dose of an antibiotic can increase a patient's risk of CDI.[60]

Additional CDI risk factors are advanced age, female sex, gastrointestinal tract surgery, immunosuppression from a medication such as chemotherapy or disease, and proton pump inhibitors. In the US and high resource settings, the majority

of deaths (80%) are associated with patients aged 65 or older.[64] This finding is likely attributable to the age at which healthcare exposure, antibiotic use, and comorbid conditions and complexity increases. For example, a recent epidemiology study in South Africa found the average age of patients testing positive for *C. difficile* was 46.5 years and the study identified tuberculosis as a novel risk factor for CDI, in a population with high HIV and tuberculosis prevalence.[62]

Treatment Considerations and Guideline Updates of *Clostridium difficile*

Historically metronidazole and vancomycin were associated with similar clinical cure and recurrence rates (metronidazole 500 mg by mouth three times daily for ten days, vancomycin 125 mg by mouth four times daily for ten days). IDSA clinical practice guidelines for CDI were updated in early 2018. These guidelines and recent evidence support initial CDI treatment with either vancomycin or fidaxomicin (fidaxomicin 200 mg by mouth twice daily for 10 days). Metronidazole shifted from previously a first line agent for mild-moderate CDI to only be used when other therapies are contraindicated or unavailable in non-severe cases (WBC ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL). Similar to the previous 2010 guidelines metronidazole is not recommend for severe CDI episodes.[56,60]

Recent evidence supports the new guidelines. For severe CDI infections, vancomycin is associated with a significant reduced risk of all cause 30-day mortality compared to metronidazole.[65] Furthermore, a 2017 Cochrane review of all severity found vancomycin was more effective than metronidazole for achieving symptomatic cure (79% vs. 72%, RR 0.90, 95% CI 0.84 to 0.97). Fidaxomicin was found to be more effective than vancomycin for achieving symptomatic cure (71% vs. 61%, RR 1.17, 95% CI 1.04 to 1.31). The authors noted the differences between the antibiotics are not great, while the cost differences between options are substantial. Ten-day CDI treatment courses were reported as: metronidazole $13, vancomycin tablets $1779, and fidaxomicin tablets $3453.[66] The cost associated with administration of the intravenous formulation of vancomycin orally is less than the capsules. A liquid vancomycin formulation was approved in 2018 and costs much less than the capsules.

Approximately 20% of successfully treated patients experience CDI recurrence, due to re-exposure or reactivation of spores, and this risk increases with each recurrence.[60,67] Recurrence risk is similar when patients are treated with vancomycin compared to metronidazole. However, clinical trials comparing fidaxomicin to vancomycin found fidaxomicin reduced risk of recurrence (15.4% vs. 25.3%) while clinical cure rate was similar. While fidaxomicin is significantly more expensive, it may be of greater benefit for patients experiencing recurrence. For patients with multiple CDI recurrences and treatment failures, fecal microbiota transplantation (FMT) is recommended and has proven to be highly effective with cure rates often greater than 90%.[60] FMT may have a role in initial CDI therapy in the future.

Additionally CDI management should include discontinuation of any antibiotics that may be contributing to CDI if clinically appropriate as soon as possible. Loperamide is contraindicated in CDI due to containment of the *C. difficile* toxins and should be discontinued if used. As with any diarrheal illness adequate rehydration and electrolyte balance is imperative. *C. difficile* spores can withstand alcohol hand sanitizer and can be transmitted between hospitalized patients and healthcare providers. Therefore, healthcare providers providing care to CDI patients should use contact precautions, gowns and gloves, and hand washing with soap and water to prevent transmission to other patients.

Role of Pharmacists in *Clostridium difficile*

Pharmacists can play a key role in CDI prevention, identification, and treatment. One of the most important roles is advocating for antimicrobial stewardship, the appropriate antibiotic use of antibiotics to reduce CDI risk and development of antimicrobial resistance. Pharmacists can review the appropriateness of antibiotic therapy and ensure antibiotics are only used when necessary. When possible, pharmacists can recommend lower risk antibiotics to reduce CDI risk. Pharmacists can also play a key role in antimicrobial stewardship programs. Stewardship interventions can include reducing the use and duration of high-risk antibiotics through formalized antibiotic restrictions and other measures. Stewardship interventions have been associated with significant reductions in CDI incidence in hospitals after epidemic outbreaks and overtime.[68]

Pharmacists should consult patients receiving an antibiotic on the risks associated with that antibiotic, including association with CDI. Pharmacist should advise patients to contact their doctor if they experience severe diarrhea or watery diarrhea that occurs three or more times per day and is not resolving. The pharmacist can also educate patients on why appropriate antibiotic use is important; antibiotic use increases the risk of antibiotic resistance development that may affect both the patient and their community.[69] Pharmacists working in transitions of care roles can ensure CDI contact precautions and treatment are continued if patients are transitioning from a hospital to long-term care setting.

CDI primary prevention vaccines are currently in development. Once approved, pharmacists can play a key role in CDI prevention by identifying patients who meet vaccination criteria and achieving high vaccination rates.[70] A phase III clinical trial is currently recruiting subjects with expected completion in 2020 (NCT03090191).

Pharmacists are commonly asked about the benefits of probiotics. While several studies have evaluated the role of probiotics in CDI, the updated IDSA guidelines state "there are insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trial".[60] The statement reflects the limitations of the meta analyses and evidence quality suggesting probiotics may be effective for preventing CDI. A Cochrane analysis concluded short-term probiotic use appears to be safe and effective, but should not be used in immunocompromised or severely

TABLE 3. Adiposity-Based Chronic Disease[73]

Diagnostic Criteria	*Disease Stage*	*Suggested Therapy*
BMI <25 kg/m2 (BMI <23 kg/m2 for certain ethnicities)	Healthy weight (no obesity)	**Primary prevention** (Healthy lifestyle)
BMI 25-29.9 kg/m2 with no complications* (BMI 23-24.9 kg/m2 for certain ethnicities)	Overweight stage 0	**Secondary prevention** (Lifestyle therapy)
BMI >30 kg/m2 with no complications* (BMI >25 kg/m2 for certain ethnicities)	Obesity stage 0	**Secondary prevention** (Lifestyle therapy; add weight-loss medications if needed for BMI >27)
BMI >25 kg/m2 with 1 or more mild to moderate complications* (BMI >23 kg/m2 for certain ethnicities)	Obesity stage 1	**Tertiary prevention** (Lifestyle therapy; add weight loss medications if needed for BMI >27)
BMI >25 kg/m2 with at least 1 severe complication* (BMI >23 kg/m2 for certain ethnicities)	Obesity stage 2	**Tertiary prevention** (Lifestyle therapy; add weight loss medications if needed for BMI >27; may consider bariatric surgery if BMI >35)

BMI – Body Mass Index
Mild/Moderate – conditions generally well controlled
Severe – conditions generally uncontrolled

**Complications include metabolic syndrome, prediabetes, type 2 diabetes, dyslipidemia, hypertension, cardiovascular disease, nonalcoholic fatty liver disease, polycystic ovary syndrome, female infertility, male hypogonadism, obstructive sleep apnea, asthma/reactive airway disease, osteoarthritis, urinary stress incontinence, gastroesophageal reflux disease, or depression*

debilitated.[71]

Pharmacists can also identify patients at risk for CDI and ensure timely testing and management. Pharmacists ensure CDI treatment prescriptions and orders are effective. For example, vancomycin CDI therapy must be administered by mouth to reach site of infection as intravenous vancomycin gut penetration is negligible. Renal adjustment is not necessary for oral vancomycin because it is not systemically absorbed. Often the intravenous formulation is administered in water orally as the oral capsules may be cost prohibitive.

Background and Epidemiology of Obesity

The national rate of obesity has been on the rise in the US over the last 40 years for adults and children.[72] National data regarding obesity rates is collected annually via the National Health and Nutrition Examination survey (NHANES). In 2015-2016, national averages indicated that 39.6 percent of adults and 18.5 percent of children were considered obese. Differing rates of obesity are seen among different demographic groups when analyzed by race and ethnicity, gender, age, socioeconomic status, highest level of education, and residential setting (urban versus rural). In the state of Wisconsin, the most recent rates of obesity collected are 32.0 percent in adults (2017), 14.7 percent in 2- to 4- year-old WIC participants (2014), and 14.3 percent in 10- to 17-year-old adolescents (2016-2017).[73]

Obesity is defined as an unhealthy level of body fat.1 Previously, obesity was determined by measuring a patient's body mass index (BMI), which is calculated as follows:

$$BMI = \frac{(\text{weight (kg)}}{[\text{height (m)}]^2}$$

In adults, patients with BMI measurements over 30 kg/m2 were considered to be obese, with patients with a BMI measuring over 40 kg/m2 classified as severely obese. For children and adolescents, obesity is determined by comparing a child's own BMI to BMI-for-age charts produced by the CDC to determine which percentile they fall in when compared to children of the same age and gender. Children in the 95th percentile and above are classified as obese, with those measuring at 120 percent of the 95th percentile and above being classified as severely obese. However, BMI is not a direct measurement for body fat, prompting more recent guidelines to further define how obesity is classified. The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) released a set of clinical practice guidelines for the diagnosis and management of patients with obesity in 2016, replacing the term obesity with the more medically-defined diagnostic term adiposity-based chronic disease (ABCD).[73] This set of guidelines also recommends that waist circumference and the related risk of comorbid conditions be evaluated, in addition to BMI, when assessing patients for the diagnosis and staging of ABCD. The staging criteria for ABCD are located in Table 3.

Primary prevention of ABCD involves promoting lifestyle factors that prevent weight gain, such as following a healthy meal plan, engaging in regular physical activity, and behavior modification.[73] Secondary prevention of patients who are diagnosed with ABCD aims to promote weight loss, prevent further weight gain, and prevent the development of weight-related comorbid conditions. Patients with obesity are at a higher risk for the development of many chronic conditions such as type 2 diabetes, hypertension and other cardiac diseases, stroke, sleep apnea, and kidney disease.[72] Lifestyle modifications are also the first-line

TABLE 4. Obesity Medications Compared[74-81]

Generic Name	Brand Name(s)	Starting Dose	Maximum Dose	Common Adverse Effects	Contraindications
Orlistat	Xenical®; Alli®	120mg three times daily; 60mg three times daily	120mg three times daily	increased defecation, fecal urgency, flatus, oily spotting, steatorrhea	chronic malabsorption syndrome, cholestasis
Lorcaserin	Belviq®, Belvix XR®	10mg twice daily; 20mg XR once daily	10mg twice daily; 20mg XR once daily	constipation, headache, hypoglycemia, nausea, dizziness, fatigue	pregnancy
Phentermine	Adipex-P®; Lomaira™	37.5mg once daily, 15mg once daily; 8mg three times daily	37.5mg once daily, 30mg once daily; 8mg three times daily	insomnia, constipation, diarrhea, headache, dry mouth	cardiovascular disease, monoamine oxidase inhibitor use, hyperthyroidism, glaucoma, history of drug abuse, pregnancy
Phentermine/ Topiramate ER	Qsymia®	3.75mg/23mg once daily	15mg/92mg once daily	constipation, dizziness, abnormal taste, insomnia, paranesthesia, dry mouth	cardiovascular disease, monoamine oxidase inhibitor use, pregnancy, glaucoma, hyperthyroidism
Naltrexone/ Bupropion	Contrave®	8mg/90mg once daily	8mg/90mg - 2 tablets twice daily	headache, dizziness, insomnia, nausea, vomiting, diarrhea, constipation, dry mouth	uncontrolled hypertension, seizure disorder, chronic opioid use, monoamine oxidase inhibitor use. Black box warning: increased suicidal thoughts or behaviors.
Liraglutide	Saxenda®	0.6mg once daily	3mg once daily	gastrointestinal upset, tachycardia, headache, dizziness, fatigue, local injection site reactions, hypoglycemia, new or worsening depression	medullary thyroid carcinoma, multiple endocrine neoplasia syndrome, pregnancy

treatment for secondary prevention, but may be supplemented with prescription medications if progress is not seen after using lifestyle modifications alone for 6 months.[73] Patients that meet predefined criteria may also be candidates for bariatric surgery; however, this topic is not a focus of this article.

Available Medications for Obesity Management

A variety of medications with varying mechanisms of action have received FDA approval for chronic weight management, many of which are newer agents that have only been introduced to the market within the last decade. As stated above, it is important to keep in mind that weight-loss medication is a second-line therapy, and lifestyle modifications should be continued in conjunction with starting any of these pharmaceutical products.

Orlistat (Xenical®) is a serotonin 2C receptor agonist indicated for chronic weight management in adults and adolescents age 12 years and older with a baseline BMI >30 kg/m2, or with a baseline BMI >27 kg/m2 with at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, and/or dyslipidemia).[74] This medication works to inhibit the activity of lipases in the stomach and small intestine and therefore prevents the absorption of dietary fats. Patients should take one 120 mg capsule orally three times daily during or up to one hour after a fat-containing meal in conjunction with a dietary management plan. An over-the-counter orlistat product, called Alli, is available as a 60 mg capsule.[75] The OTC packaging instructs patients to take one 60 mg capsule orally with a fat-containing meal, not to exceed more than three capsules daily (180 mg). Patients taking orlistat concomitantly with cyclosporine or levothyroxine should separate these medications by three and four hours from doses of orlistat, respectively. The most common adverse effects seen during use of this medication are increased defecation and fecal urgency, flatus, oily spotting and steatorrhea.

Lorcaserin (Belviq®) is another serotonin 2C receptor agonist approved for use in weight management in adults with a baseline BMI >30 kg/m2, or with a baseline BMI >27 kg/m2 with at least one weight-related comorbid condition.[76] The recommended dose of the immediate-release formulation is 10 mg orally twice daily. Lorcaserin is also available as an extended-release formulation (Belviq XR®), which is available as a 20 mg oral tablet that is taken once daily. Either formulation may be taken with or without food, and the extended-release tablets should not be crushed or chewed. Lorcaserin is classified as a class IV controlled substance in the US based on its potential for abuse; therefore, its use should be avoided in patients with a history of substance abuse. Patients who have not seen greater than or equal to 5 percent weight loss compared to baseline after 12 weeks of therapy should discontinue use (either formulation). This medication should be used with caution in patients with renal or hepatic impairments, but no specific dose adjustments are recommended by the manufacturer. Lorcaserin and lorcaserin extended-release should not be used during pregnancy (category X). The most common side effects of this medication are constipation, headache, hypoglycemia (in diabetic patients), nausea, dizziness, and fatigue. Patients should also be cautious and monitor for signs and symptoms of serotonin syndrome if using lorcaserin/

lorcaserin extended-release concomitantly with other serotonergic agents (bupropion, monoamine oxidase inhibitors, serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, triptans, etc.).

Phentermine (Adipex-P®) is a noradrenergic agent approved for short-term treatment of obesity in adults and adolescents age 16 years and older in combination with lifestyle modifications.[77] Phentermine is available as generic 37.5 mg tablets (37.5 mg taken orally once daily in the morning) or 15 mg capsules (15-30 mg taken orally once daily in the morning). An 8 mg oral tablet is also available (Lomaira™) and should be taken orally three times daily.[78] Phentermine works to increase endogenous norepinephrine and dopamine, which promotes weight loss through an increased resting metabolic rate and suppressed appetite. Dose adjustments should be provided for patients with renal impairment, and should not be used in pregnancy. Phentermine is classified as a class IV controlled substance in the US based on its potential for abuse; therefore, its use should be avoided in patients with a history of substance abuse. The most common adverse effects seen with use of this medication are insomnia, constipation, diarrhea, headache and dry mouth.

Phentermine is also available as a combination product with a second noradrenergic agent, topiramate extended-release (ER; Qsymia®), for chronic weight management in adults with a baseline BMI >30 kg/m2, or with a baseline BMI >27 kg/m2 with at least one weight-related comorbid condition.[79] Patients are initiated on the medication by taking one phentermine 3.75 mg/topiramate ER 23 mg capsule orally once daily for 14 days, and are then increased to a maintenance dose of one phentermine 7.7 mg/topiramate ER 46 mg capsule once daily. After 12 weeks, if patients have not lost at least 3 percent of baseline weight, use should be discontinued or increased to one phentermine 11.25 mg/topiramate ER 69 mg capsule once daily for 14 days, and then increase further to one phentermine 15 mg/topiramate ER 92 mg capsule once daily for 12 weeks. If at least 5 percent of baseline body weight has not been lost since dose escalation, therapy should be discontinued by de-escalating the dose to one capsule every other day for one week. Dose adjustments should be performed in the setting of renal and/or hepatic impairments. The most common adverse effect seen with this combination therapy are constipation, dizziness, abnormal taste, insomnia, paresthesia and dry mouth. Patients with a history of cardiovascular disease, including coronary artery disease, stroke, arrhythmias, congestive heart failure or uncontrolled hypertension should not be prescribed any product containing phentermine.[79]

A combination product containing naltrexone (an opioid antagonist) and bupropion (a norepinephrine and dopamine reuptake inhibitor) is indicated for chronic weight management in adults with a baseline BMI >30 kg/m2, or with a baseline BMI >27 kg/m2 with at least one weight-related comorbid condition.[80]

Although the exact mechanism of this product is not understood, it is likely that it exerts effects on multiple areas of the brain, including the reward system, to regulate appetite and aid in weight loss. Available as brand name Contrave®, this medication is initiated at one naltrexone 8 mg/ bupropion 90 mg tablet orally in the morning for one week. Then, doses are increased to one tablet twice daily for one week; then, two tablets in the morning and one tablet in the evening for one week. A maintenance dose of two tablets in the morning and two tablets in the evening is taken daily thereafter. Patients who do not see a weight loss of at least 5 percent from baseline after using the maintenance dose for 12 weeks should discontinue use. Dose adjustments should be performed for patients using this medication in the setting of renal or hepatic impairment. Patients should be advised that this product carries a black box warning for the potential to cause increased suicidal thoughts or behaviors. The most common adverse effects of this medication are headache, dizziness, insomnia, nausea, vomiting, diarrhea, constipation and dry mouth.

Liraglutide (Saxenda®) is a human glucagon-like peptide-1 (GLP-1) receptor agonist that has received FDA approval for the management of obesity in adult patients with a baseline BMI >30 kg/m2, or with a baseline BMI >27 kg/m2 with at least one weight-related comorbid condition.[81] Liraglutide is also approved for use in the management of type 2 diabetes (Victoza), but the products are not interchangeable between indications. In terms of weight management, endogenous GLP-1 works in the body to slow gastric emptying, which decreases caloric intake by promoting feelings of satiety. Liraglutide is used as a once-daily subcutaneous injection, initiated at a starting dose of 0.6 mg daily. The daily dose should be increased by 0.6 mg increments at weekly intervals until a maintenance dose of 3 mg daily is achieved. Daily injections should be administered into the abdomen, thigh or upper arm without regards to meals. Patients that do not see greater than or equal to 4 percent weight loss compared to baseline after 16 weeks should discontinue use. Since liraglutide delays gastric emptying, the potential for impacts on absorption of oral medications should be monitored. Common adverse effects include gastrointestinal upset (such as nausea, vomiting, diarrhea or constipation, abdominal pain, decreased appetite, and/or dyspepsia), tachycardia, headache, dizziness, fatigue, local injection site reactions (such as redness, itching or rash), hypoglycemia (especially when used in combination with sulfonylureas in patients with diabetes), and new or worsening depression or suicidal behaviors. This medication carries a Black Box Warning for the risk of development of thyroid t-cell tumors, and should not be used in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Liraglutide use is also contraindicated in pregnancy and should be used with caution in patients with renal or hepatic impairments.

The Pharmacist's Role in Obesity Management

Pharmacists are often considered one of the most accessible healthcare providers due to their presence in the retail setting and are adequately trained to assist patients in achieving their weight loss goals. One of the ways that pharmacists can help patients looking to lose weight is to assist them in the development of healthy eating and exercise plans. First, patients should be engaged in motivational interviewing to determine their readiness to make a change. Once a patient is ready to implement lifestyle modifications, pharmacist can assist patients with development of their plan. The current set of AACE and ACE guidelines recommend that patients attempting weight loss begin a reduced-calorie meal plan, participate in 150 minutes of aerobic physical activity over three to five days per week, and modify their behaviors (such as self-monitoring of food intake and goal setting) to achieve weight loss.[67] Pharmacists are also in a great position to provide ongoing support and encouragement to patients throughout their weight loss journey, as most pharmacists will see patients every one to three months when they visit the pharmacy to obtain medication refills.

Pharmacists are also able to provide patients initiating weight loss medication therapy with appropriate medication counseling to supplement information that their provider may have already shared with them. Medication counseling for these types of medications should always include administration directions (i.e. with or without food, or injection technique for liraglutide), adverse effects and how to manage them, and monitoring parameters (i.e. when they should expect to see results, or certain parameters that should be monitored for safe and effective use). Pharmacists in both the inpatient and outpatient setting may also receive postoperative medication inquiries from patients or other healthcare providers when patients undergo weight loss surgeries. For example, the absorption of certain medications may be affected and a patient's medication regimen may need substituting and/or adjusting of therapies to accommodate these physiological differences. Nutritional supplements are also an area in which pharmacists can provide support to postoperative patients, as they will also be less able to obtain these nutrients from their diet after surgery.

Summary of Obesity Epidemic

Obesity rates have continued to climb to alarming rates in the US, with national rates mirrored in Wisconsin. Recently updated guidelines promote well-defined methods for diagnosing, classifying and managing ABCD. There are many different medication options available to patients that are not able to be managed through lifestyle modifications alone. Pharmacists are the most accessible healthcare providers in the community and are adequately trained to provide patients with education and support as they work towards accomplishing their weight management goals.

Conclusion

Opioid abuse, CDI and obesity are three epidemics that are currently affecting the State of Wisconsin and the US. This article has shown ways in which pharmacists are uniquely positioned to help combat these epidemics through a variety of mechanisms.

Cody Wenthur is an Assistant Professor at the University of Wisconsin-Madison School of Pharmacy in Madison, WI. Laurel Legenza is the Director of Global Health & Assistant Scientist at the University of Wisconsin-Madison School of Pharmacy in Madison, WI. Nicole Weinfurter is a 4th Year Doctor of Pharmacy Candidate and Dean Bowen is a 3rd Year Doctor of Pharmacy Candidate at the University of Wisconsin-Madison School of Pharmacy in Madison, WI.

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Assessment Questions

1. The CDC defines an epidemic as, "a gradual and often minor increase in the number of cases of a disease above what is normally expected in that population area."
   a. True
   b. False

2. What was the approximate mortality rate per 100,000 individuals due to opioid overdose in Wisconsin in 2016?
   a. 26.2
   b. 20
   c. 20,600
   d. 827

3. A key principle of current guidelines for opioid prescribing is 'start with a low dose and increase dosage rapidly'.
   a. True
   b. False

4. Patient counseling on naloxone kits for opioid overdose should include which of the following topics?
   a. Overdose risk factors
   b. Overdose response measures
   c. Administration instructions
   d. All of the above

5. What class of antibiotics is associated with a high CDI risk?
   a. Fluoroquinolones
   b. Macrolides
   c. Sulfonamides-trimethoprim
   d. Penicillins

6. According to the CDC, CDI is associated with 453,000 infections per year and about 15,000 of these infections result in death directly attributable to CDI.
   a. True
   b. False

7. Which of the following is NOT a way pharmacists can help combat the CDI epidemic?
   a. Recommend lower risk antibiotics
   b. Educate patients receiving an antibiotic on the risks associated with that antibiotic, including association with CDI
   c. Become involved with antimicrobial stewardship
   d. Always recommend probiotics

8. What was the rate of obesity for adults in the state of Wisconsin in 2017?
   a. 14.7%
   b. 18.5%
   c. 32.0%
   d. 39.6%

9. What is the most common monitoring parameter to measure efficacy of prescription weight loss medications?
   a. Body-mass index (BMI)
   b. Percentage of weight loss from baseline after a specified time period
   c. Development of weight-related complications
   d. Daily calorie intake

10. Which of the following are common side effects of medications available for chronic weight management?
    a. Gastrointestinal upset (nausea/vomiting, constipation and/or diarrhea)

b. Dizziness or fatigue
c. Headache
d. All of the above

11. Which of the following are ways that a pharmacist can help patients reach their personal weight management goals?
    a. Provide adequate medication counseling for medications used in chronic weight management
    b. Engage patients using motivational interviewing techniques to assess readiness to make lifestyle modifications
    c. Provide education and aid patients in monitoring for other weight-related health complications (e.g. diabetes, hypertension, etc.)
    d. All of the above

12. Did the activity meet the stated learning objectives? (if you answer no, please email sarahs@pswi.org to explain)
    a. Yes
    b. No

13. On a scale of 1 – 10 (1-no impact; 10-strong impact), please rate how this program will impact the medication therapy management outcomes or safety of your patients.

14. On a scale of 1 – 10 (1-did not enhance; 10-greatly enhanced), please rate how this program enhanced your competence in the clinical areas covered.

15. On a scale of 1 – 10 (1-did not help; 10-great help), please rate how this program helped to build your management and leadership skills.

16. How useful was the educational material?
    a. Very useful
    b. Somewhat useful
    c. Not useful

17. How effective were the learning methods used for this activity?
    a. Very effective
    b. Somewhat effective
    c. Not effective

18. Learning assessment questions were appropriate.
    a. Yes
    b. No

19. Were the authors free from bias?
    a. Yes
    b. No

20. If you answered "no" to question 19, please comment (email info@pswi.org).

21. Please indicate the amount of time it took you to read the article and complete the assessment questions.

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