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

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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

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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]

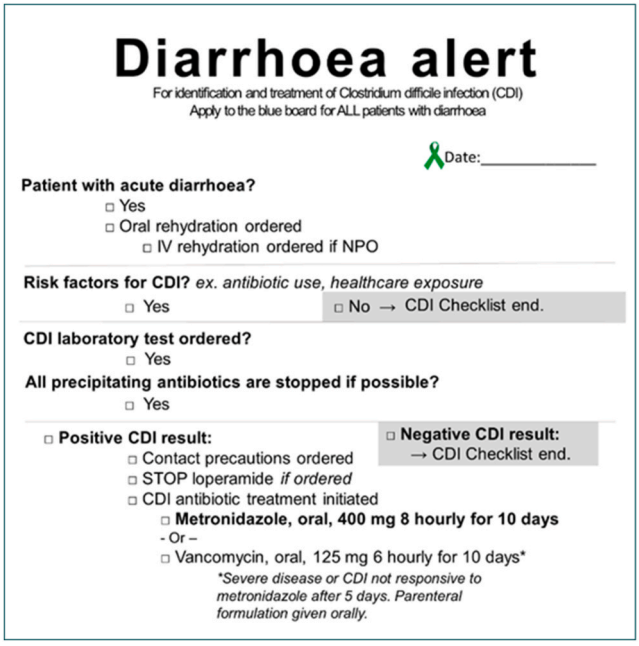
2. Methods

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



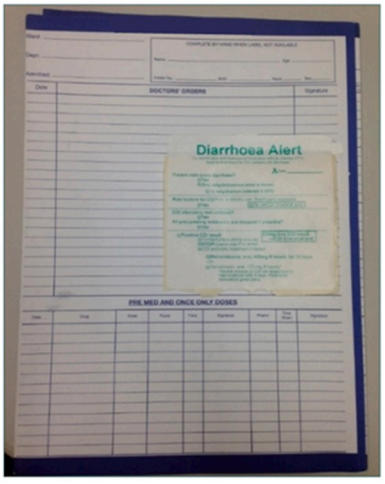


Fig. 1. CDI intervention checklist* and CDI checklist applied to medical record order form
*Treatment follows the 2015 South African Standard Treatment Guidelines in place at the time the checklist was developed. The 2019 guidelines now specify metronidazole for treatment of mild to moderate *Clostridioides 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.

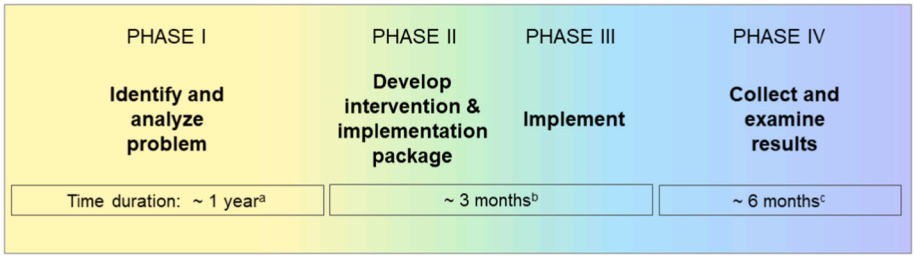


Fig. 2. Study design in four project phases
a. Estimated total time includes time to develop protocol and obtain research ethics approval. b. Estimated total time on site at hospitals preparing and implementing intervention. c. Estimated total time collecting and analyzing 90-day post-implementation 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

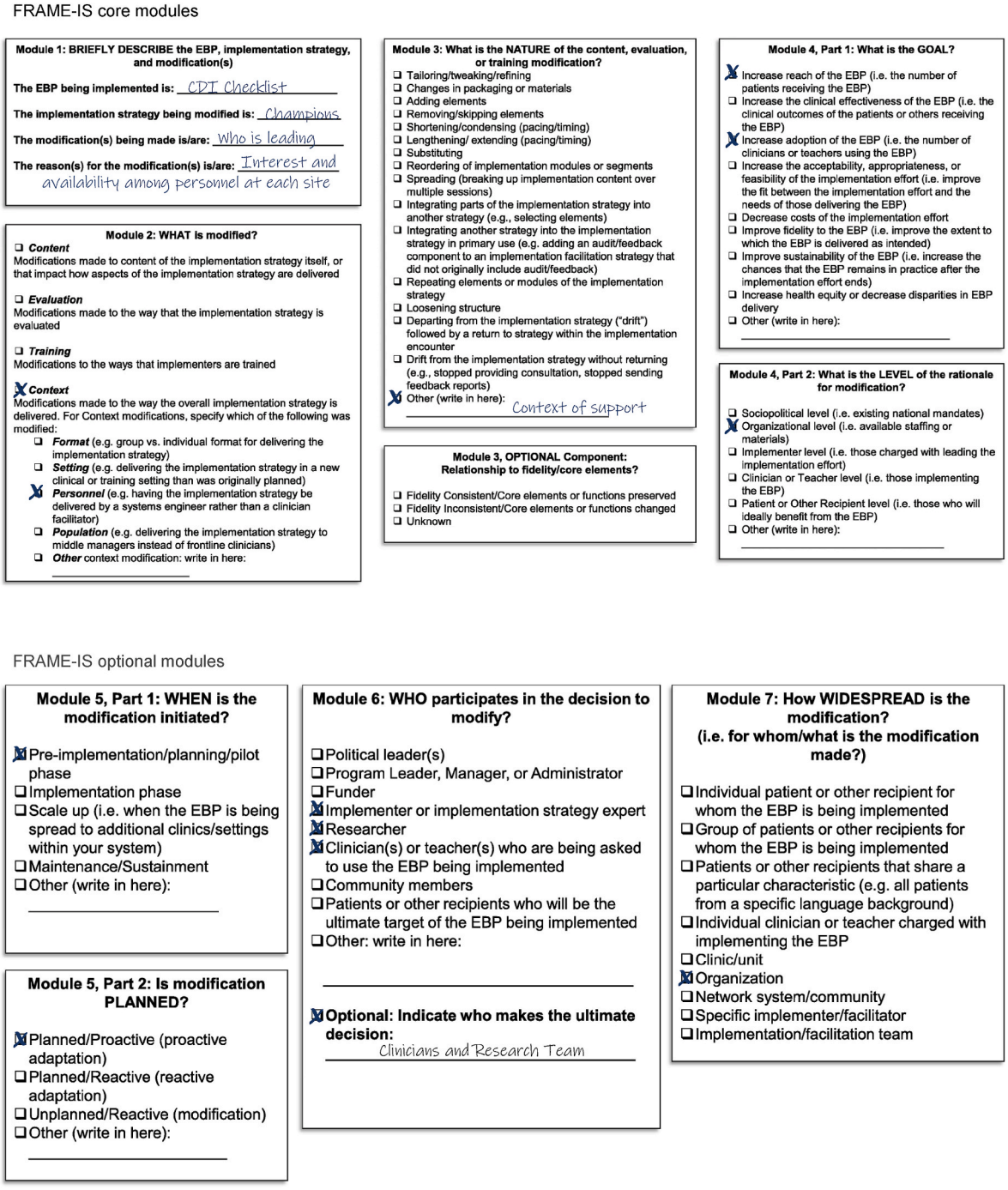


Fig. 3. Adaptations to the champions implementation strategy contextualized within the Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies (FRAME-IS)[a].
a. Applied FRAME-IS adapted from Miller et al. *Implementation Science* 2021.

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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Appendix. Supplementary data

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