Review:

Clostridium difficile: a healthcare associated infection of unknown significance in adults in sub-Saharan Africa.

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Abstract:

Background:

Clostridium difficile infection (CDI) causes a high burden of disease in high-resource healthcare systems, with significant morbidity, mortality and financial implications. CDI is a healthcare-associated infection for which the primary risk factor is antibiotic usage and it is the leading cause of bacterial diarrhoea in HIV infected patients in USA. Little is known about the disease burden of CDI in sub-Saharan Africa, where HIV and healthcare associated infection have a higher prevalence and antibiotic usage is less restricted.

Aim:

To review published literature on CDI in sub-Saharan Africa, highlighting areas for future research.

Methods:

English language publications since 1995 were identified from online databases (PubMed, Medline, Google Scholar, SCOPUS) and personal collections of articles, using combinations of keywords to include *C. difficile,* Africa and HIV..

Results:

Ten relevant studies were identified. There is considerable variation in methodology to assess for carriage of toxigenic *C. difficile* and its associations. Eight studies report carriage of toxigenic *C. difficile.* Three (of four) studies found an association with antibiotic usage. One (of four) studies

showed an association with HIV infection. One study showed no association with degree of immunosuppression in HIV. Two (of three) studies showed an association between carriage of toxigenic *C. difficile* and diarrhoeal illness.

Conclusion:

Whilst the carriage of toxigenic *C. difficile* is well described in sub-Saharan Africa, the impact of CDI in the Region remains poorly l understood and warrants high quality research.

Keywords:

Clostridium difficile, sub-Saharan Africa*,* diarrhoea, HIV, antibiotics

Introduction:

Clostridium difficile, an anaerobic Gram-positive spore-forming bacterium, was first described in neonatal gut, and was initially presumed to be a commensal organism in 1935.[1] Later, it was recognised to cause pseudomembranous colitis via toxin production and it has since emerged as a major enteric pathogen.[2, 3] Its clinical significance ranges from asymptomatic carriage to life threatening colitis, with significant associated morbidity and mortality. *C. difficile* colonises the large bowel following ingestion of spores, which are heat and acid resistant.[4] The spores can be found in all healthcare settings and in the general environment. [5, 6] Gut damage in susceptible individuals results from production of two exotoxins, TcdA and TcdB, whose action is cytotoxic.[7] The emergence of the 027/BI/NAP1 strain, with

dramatically increased cytotoxin production, is responsible for the observed increased prevalence and virulence of *C. difficile* in recent years.[8-10] This strain emerged in North America and Western Europe and rapidly disseminated worldwide.[11]

The primary risk factor for *C difficile* infection (CDI) is antibiotic usage. CDI is known to be the cause of up to 25% of antibiotic associated diarrhoea.[12] CDI was originally described following clindamycin use but is now known to complicate the use of many broad spectrum antibiotics, particularly cephalosporins, co-amoxiclav and fluoroquinolones.[3, 13] Following antibiotic usage, there is an imbalance in the normal gut flora and *C. difficile* overgrowth can lead to pseudomembranous colitis in susceptible individuals.[14] Other described risk factors for CDI include hospital admission, exposure to an infected carrier, advanced age and immunosupression.[15]. The importance of proton pump inhibitors and of other interventions that reduce the gastric acid barrier in increasing susceptibility to CDI remains controversial. [16, 17] There is a described relationship between CDI and HIV in USA where it is known to be the leading cause of bacterial diarrhoea in HIV-infected populations, but it is not clear how much this reflects increased exposure to healthcare compared to HIV negative individuals.[18, 19] Only two studies show a convincing associated between CDI and low CD4 count, and interpretation of these results is difficult given the high rates of *C. difficile* colonisation in HIV infected populations.[19-22]

While CDI has been extensively researched in well-resourced health systems, there are few published studies about CDI in sub-Saharan Africa. It is known that healthcare associated infections cause a greater disease burden in healthcare systems with fewer resources.[23] Furthermore the main risk factor for CDI is antibiotic usage and in sub-Saharan Africa there is widespread availability of broad-spectrum antibiotics and fewer controls on their usage.[24] Finally, HIV is far more prevalent in sub-Saharan Africa than in USA or Europe. It is, therefore, possible that CDI plays an important role in diarrhoeal illness in sub-Saharan Africa, yet there are very few published data on the subject. Published infection rates vary greatly, with some authors describing 0% prevalence in Kenya and Zambia, whilst the highest published rate is from Nigeria at 43%.[25-27] The nature of the relationship between HIV and CDI in sub-Saharan Africa remains poorly understood.

The aim of this review is to describe current published literature regarding CDI in adults in Sub-Saharan Africa and to highlight areas warranting further research.

Clostridium difficile Infection in Sub-Saharan Africa:

In order to identify studies assessing CDI in adults in sub-Saharan Africa we performed a literature search for "*Clostridium difficile*" AND "Africa" in PubMed and Scopus. All relevant papers in English from 1995 onwards were included in the review and their bibliographies were reviewed for relevant papers. Papers looking at adults and children were only included if it was possible to

distinguish between the two populations. In total ten relevant studies were found. Data were extracted from relevant papers using a standardised proforma.

Results:

Ten studies looked for toxigenic *C. difficile* carriage in sub-Saharan Africa. Of these, eight describe toxigenic *C.difficile* carriage. There is considerable variation in laboratory methodology used to identify *C. difficile* and in the populations studied. Furthermore there is wide variation in the methodology used to assess the association of CDI with recent antibiotic usage, with HIV, with presence of symptoms of diarrhoea, and with degree of immunosupression. Table 1 summarises current published studies of CDI in adult populations in different countries in Sub-Saharan Africa.

Discussion:

The majority of published studies, and all studies after the year 2000, describe carriage of toxigenic *C. difficile* in adult populations in sub-Saharan Africa. In three studies, which assessed recent antibiotic exposure, there was a significant association between antibiotic exposure and CDI, however no studies were designed to implicate individual antibiotics.[29, 30, 34] These findings are consistent with the well-described risk factor of antibiotic usage in high resourced healthcare systems. In three of four studies, which assessed association with HIV status, no association was found. The only study

claiming an association between HIV status and CDI was from Nigeria and has significant methodological flaws, which require the conclusions to be viewed with caution.[27] The lack of association between CDI and HIV status differs from observations in high-resource healthcare systems.[18, 20, 21] The only study to assess the association between degree of immunosuppression in HIV and CDI is from Malawi.[31] It showed no significant association between carriage of toxigenic *C. difficile* and severe immunosuppression (CD4 cell counts <50 x 10^6/L), although numbers in this group were small. This warrants assessment in a larger study population. The disease burden of CDI in sub-Saharan Africa, particularly in areas of high HIV prevalence, has yet to be well characterized and warrants further research.

A further area of uncertainty is the role that *C. difficile* plays in diarrhoeal illness, as opposed to asymptomatic infection and incidental detection, in populations studied in sub-Saharan Africa. Table 1 shows that a wide variety of laboratory methods have been used to detect C difficile in the different studies, with different sensitivities and specificities. Methods that use cytotoxicity or immunogenic assays to detect *C. difficile* toxin, reliably detect invasive CDI but sensitivity is variable and dependant on laboratory technique, while PCR based methods used alone probably result in overdiagnosis.[35-38] Only one study used the two step diagnostic algorithms currently recommended in many countries, using assays for faecal *C difficile* glutamate dehydrogenase (GDH) as a screening test for presence of infection followed by confirmatory PCR for cytotoxin genes to diagnose invasive disease potential. [35] The majority of studies assessed *C. difficile* in patients

with diarrhoea and did not compare these to non-diarrhoeal controls. However the most robust study of CDI in sub-Saharan Africa showed a clear association between detection of toxigenic *C. difficile* and symptomatic diarrhoeal illness in South Africa.[29] Another study of adults and children in Tanzania detected toxigenic *C. difficile* in 9 of 141 subjects with diarrhoea compared to none in the stools of 109 symptom free controls.[34] Whilst asymptomatic carriage has been well documented and demonstrated to contribute to ongoing transmission of *C. difficile* in well-resourced healthcare systems, its significance in sub-Saharan Africa remains to be characterised altogether. [21, 22, 39, 40]

Only one study on CDI in South Africa described outcomes.[33] There was an observed 66.7% mortality rate for patients with CDI and diarrhoea. However there was no statistical difference in mortality between patients with or without *C. difficile*, nor in length of stay and intensive care admission. Twelve percent of patients with CDI required colectomy, a finding that was significantly associated with the presence of toxigenic *C. difficile*. Whilst the presence of toxigenic *C. difficile* has been described in sub-Saharan Africa, its extent and clinical significance remain poorly understood.

Conclusion:

There are relatively few studies on CDI in sub-Saharan Africa, but toxigenic *C. difficile* has been detected in the majority of studies designed to look for it in the region, where it is consistently associated with antibiotic exposure. Further high quality research is needed to define the epidemiology of CDI in sub-Saharan Africa in order to clarify the extent of colonisation within community and hospitalised populations, the extent to which CDI is associated with HIV and CD4 count, and its role in contributing to morbidity and mortality.

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epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. *Clin Infect Dis.* October 15, 2007 2007;45(8):992-998.

Table 1. Published studies on CDI in adults in sub-Saharan Africa. 1995 – present.

Author	Year	Country	Setting	Controls	Diagnostic test for CDI	Study size (adults)	CDI Prevalence (adults)	Antibiotic association	HIV association
Mwachari[25]	1998	Kenya	HIV positive adult inpatients with chronic diarrhoea	n/a	Cytotoxicity assay	75	0%	n/a	n/a
Germani[28]	1998	Central African Republic	Adults presenting to hospital with diarrhoea	HIV positive and negative non-diarrhoeal adult inpatients	Cytotoxicity assay	430	0.7%	n/a	n/a
Zulu[26]	2000	Zambia	HIV positive adult inpatients	n/a	ELISA for toxin A	68	0%	n/a	n/a
Samie[29]	2008	South Africa	Adults and children in hospital and community with diarrhoea	HIV positive and negative non-diarrhoeal adult in hospital and community	PCR for cytotoxin genes	135	17.8%	Yes	No
Onwuema[27]	2011	Nigeria	Adults and children in hospital and community with diarrhoea	HIV negative (or unknown) adults in the community	EIA for toxin A and B	140	4.3% to 43.5%	n/a	Yes
Rajabally[30]	2013	South Africa	Adult inpatients with diarrhoea	n/a	EIA for toxin A	643	9.2%	Yes	No
Beadsworth[31]	2014	Malawi	Adult inpatients with diarrhoea	HIV positive and negative non-diarrhoeal adult inpatients	ELISA for toxin A and B	206	13.6%	n/a	No
Simango[32]	2014	Zimbabwe	Adults and children in community with diarrhoea	n/a	Culture and EIA for toxin A and B	159	6.9%	n/a	n/a
Kullin[33]	2015	South Africa	Adults in hospital and community with diarrhoea	n/a	PCR for cytotoxin genes	156	16%	n/a	n/a
Seugendo[34]	2015	Tanzania	Adults and children inpatients with diarrhoea	Non-diarrhoeal adults in community	Rapid test for GDH and PCR for cytotoxin genes	33	9.1%	Yes	n/a

Key: CDI = *Clostridium difficile* infection, ELISA = Enzyme linked immunosorbent assay, PCR= polymerase chain reaction, EIA = Enzyme immunoassay, n/a = not assessed, GDH= glutamate dehydrogenase (*Clostridium difficile* specific).