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A comparative evaluation of toxigenic Clostridioides difficile prevalence as a metric of hospital antibiotic stewardship in Saudi Arabia

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A COMPARATIVE EVALUATION OF TOXIGENIC CLOSTRIDIOIDES DIFFICILE PREVALENCE AS A METRIC OF HOSPITAL ANTIBIOTIC STEWARDSHIP IN SAUDI ARABIA

Submitted by Christopher Okeahialam

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Abstract

Background

Clostridioides difficile infection (CDI) is caused by toxigenic strains of C. *difficile* a Gram-positive, antibiotic resistant anaerobic bacillus. Reports suggest that CDI and associated risk factors including inappropriate exposure to antibiotics, are common in Saudi Arabia. The aim of this study was to assess the impact of antibiotic stewardship on the prevalence of toxigenic C. *difficile* (tCd) among inpatients at Johns Hopkins Aramco Healthcare in Saudi Arabia and evaluate the utility of tCd prevalence as a patient outcome metric of antibiotic stewardship.

Methods

A retrospective review of laboratory data was conducted to identify patients testing positive for toxigenic C. *difficile* over the study period. The prevalence of tCd among inpatients tested pre and post implementation of the antibiotic stewardship program, was compared to assess the impact of the program.

Result

A significant reduction in tCd prevalence was observed following the implementation of the antibiotic stewardship program.

Conclusion

The prevalence of toxigenic C. *difficile* can be used as a simple and sensitive metric of the impact of hospital antibiotic stewardship on CDI. Formulary restriction of high CDI risk antibiotics and bundling of antibiotic prescribing and infection control interventions will strengthen the impact of antibiotic stewardship in reducing tCd prevalence in the hospital.

Acknowledgments and Dedication

I would like to acknowledge the diligent supervisory input of Dr. A. Bolhuis, and the support of Dr. A. Rabaan in facilitating the collation of the laboratory data on toxigenic C. *difficile*.

This is dedicated to my wife Ebere for her belief, fortitude, numerous cups of tea and sense of humor through what was at times an arduous journey for both of us, our lovely daughter Chiamanda (the best gift of 2019), and my parents for their encouragement through the years and being there to remind me of childhood, when nothing seems impossible.

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List of Abbreviations

ASP	Antibiotic Stewardship Program
CCA	Cell cytotoxicity assay
CDAD	*Clostridioides difficile* associated disease
CDI	*Clostridioides difficile* infection
DDD	Defined daily dose
EIA	Enzyme linked immunosorbent assay
GDH	Glutamate dehydrogenase
IDSA	Infectious Disease Society of America
NAP	North American Pulsed Field
NAAT	Nucleic Acid Amplification Test
PCR	Polymerase chain reaction
SHEA	Society for Healthcare Epidemiology of America
SMA	Self-medication with antibiotics
tCd	Toxigenic *Clostridioides difficile*
WHO	World Health Organization

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CHAPTER 1 Background

Antibiotics have contributed immensely to reducing infectious disease morbidity and mortality. The popularity of antibiotics is evidenced by ecological studies (Van Boeckel *et al* 2014, Klein *et al* 2018) showing an increase in global antibiotic consumption between the years 2000 and 2015. Unfortunately, antibiotic use has been accompanied by unintended consequences. Over time, the combined pressure of judicious and non-judicious use of these agents in human and animal healthcare has led to microbial adaptation, and provided a selective advantage for the propagation of multi-drug resistant strains. This association between antibiotic use and microbial resistance has been observed in hospital and community settings (Costello *et al* 2010, Bell *et al* 2014). The impact has been a decline in the clinical efficacy of a broad range of antibiotic groups and an increase in infectious disease morbidity and mortality (WHO 2014).

1.1 Antibiotic Stewardship

The growing burden of antibiotic-resistant infections has prompted recommendations from the World Health organization (WHO) and other international bodies for the institution of antibiotic stewardship programs in health care settings. Antibiotic stewardship has been defined as “coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents, by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration” (Fishman 2012). These interventions have been categorized as core and supplemental by the infectious disease society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA, Dellit *et al* 2007). The core strategies are *formulary restriction and preauthorization* of antibiotic use, *and prospective audit of*

prescriptions with real-time feedback to prescribers. Supplemental strategies include *prescriber education*, *antibiotic usage guidelines* and *clinical pathways*, *antibiotic cycling* and scheduled *antibiotic switch*, *streamlining or de-escalation* (switching from broad to narrow spectrum antibiotics), use of *antibiotic order forms*, *dose optimization*, *parenteral to oral conversion*, and *computer-assisted decision support* (Dellit *et al* 2007).

The strategy of formulary restriction and preauthorization gives the antibiotic stewardship team greater control of antibiotic use in the healthcare facility, since prescribers must seek approval if they wish to use one or more restricted antibiotics. On its own however this strategy may not engender the relationships between prescribers and the antibiotic stewardship program that is necessary for sustainability and long term effectiveness.

Prospective audit and feedback, the other core strategy, involves the ongoing review of patients receiving antibiotics, by the antibiotic stewardship team. Prescribers receive "unsolicited" feedback including recommendations to change the type, dose or duration, or route of administration of antibiotics. The strength of this strategy is that physician autonomy is preserved, and it provides a medium for dialogue and education on appropriate antibiotic use. However, an important weakness is that prescriber compliance with the recommendations of the stewardship team is optional. Relying on this strategy alone may limit the impact of the antibiotic stewardship program.

Antibiotic stewardship is fundamentally about influencing prescribing behavior. The preceding considerations of the relative strengths and weakness of the IDSA-

recommended core strategies illustrate the human factors that often need to be addressed in interventions requiring behavioral change. The importance of prescriber compliance as a determinant of antibiotic stewardship success is highlighted by a number of studies (Mol *et al* 2004, De Souza *et al* 2006, Cortoos *et al* 2008, Aldeyab *et al* 2009, and Charani *et al* 2013). These studies jointly suggest the existence of a professional hierarchy influencing the way antibiotics are prescribed in hospitals, and a culture of autonomy led by senior physicians in which personal knowledge and experience over-ride antibiotic prescribing guidelines. Charani *et al* (2013) describe a "prescribing etiquette" among physicians that advocates non-interference in the practice of colleagues. This seemingly, would be at odds with the persuasive nature of prospective audit and feedback, and the restraints of formulary restriction/pre-authorization.

The need among prescribers to preserve their autonomy is further illustrated by the study of La Rosa *et al* (2007), who observed that physicians intentionally delayed prescribing until pre-authorization was no longer required (10pm), and by so doing were able to bypass the bottleneck of the stewardship program. This phenomenon has been described as "stealth dosing" (La Rosa *et al* 2007). These observations of a prescribing hierarchy, norms and etiquette, and a desire for autonomy is consistent with the "social/professional role and identity" domain of the theoretical domains framework (TDF) described by Cane *et al* (2012).

Preserving autonomy in prescribing also appears to be related to 'emotion' which is another TDF domain. Schouten *et al* (2007) observed that prescriber anxiety regarding

clinical outcomes of their patients often over-rides the potential risk of adverse consequences of antibiotic use. Similarly, a systematic review of 46 studies predominantly from North America and Europe (Lopez-Vazquez *et al* 2012) identified complacency (fulfilling patient's expectations) and fear of patients developing complications as important drivers of antibiotic prescribing.

The level of prescriber buy-in appears therefore to be an important consideration when evaluating the impact of antibiotic stewardship in a given setting.

1.2 Antibiotic Stewardship Metrics

Comparative evaluations of the impact of antibiotic stewardship interventions are hindered by a lack of standardized metrics. Four metric categories have been identified to date. These are antibiotic utilization, costs, patient outcomes (mortality, length of stay, infections), and processes (such as prescribing practices, compliance with guidelines, de-escalation from broad to narrow spectrum antibiotics). Evaluation of stewardship interventions have tended to focus on the impact on antibotic consumption, cost and prescribing practices (Septimus 2014, Dodds *et al* 2014). It is generally accepted that for stewardship interventions to be supported and sustained, cost-considerations are inevitable. However, measuring changes in cost or prescribing practices says little of the impact of the program on preventing antibiotic-resistant infections, which afterall is the original intent of antibiotic stewardship.

Measuring the impact of stewardship on antibiotic resistant infections may be challenging however. Septimus (2014) highlights some of the constraints. One is that changes in the

rate of antibiotic resistance in a hospital (or other healthcare setting) may reflect the influence of factors other than the antibiotic stewardship program, including ongoing infection prevention and control interventions in the hospital. It may also be difficult to distinguish antibiotic resistant infections attributable to antibiotic exposure within the hospital from those due to exposure in the community.

Clostridioides difficile associated disease (CDAD) is caused by toxigenic strains of C. *difficile*, a Gram-positive, spore forming, antibiotic resistant anaerobic bacillus. The disease spectrum ranges from asymptomatic colonization of the gut to infection.

Clostridioides difficile infection (CDI) is the most common cause of nosocomial antibiotic-associated diarrhea in Europe and North America and considered not only an *urgent antimicrobial resistance threat* (CDC, 2013) but also an adverse outcome of antibiotic use in healthcare. Among the antibiotic resistant infections, CDI has been observed to be especially responsive to antibiotic stewardship interventions. For this reason, Graber (2017) in a commentary on the significant impact of antibiotic restriction on the rate of CDI in a Scottish health board (Lawes *et al* 2015), suggests that CDI is perhaps *stewardship's lowest hanging fruit*. It appears to be an ideal metric for evaluating the impact of antibiotic stewardship on both antibiotic resistance and patient safety.

1.3 *Clostridioides difficile* infection

C. *difficile* infection may manifest as mild to severe diarrhea, pseudomembranous colitis, toxic megacolon, colonic perforation, sometimes resulting in death (Gerding *et al*, 1995). C. *diffiicile* pathogenicity is expressed by the production of one or both of two toxins (A

and/or B). Some C. *difficile* strains also express a third “binary” toxin (Schwan *et al* 2009, Burke and Lamont 2014). Toxigenic strains are identified either by laboratory culture, toxigenic assay, Enzyme immuno Assay (EIA) or polymerase chain reaction (PCR) to identify the genes encoding toxins A or B.

Transmission of C. *difficile* is via the fecal oral route through the ingestion of spores.

This may occur directly (person to person) or indirectly through contact with contaminated environmental fomites.

The US centre for disease control has developed surveillance definitions for three categories of CDI based on the time of symptom onset. These are health-care acquired (nosocomial), community-acquired or indeterminate CDI. CDI with a symptom onset more than 48 hours after hospital admission or less than 4 weeks after discharge is considered to be healthcare acquired, while CDI with symptom onset in the community, within 48 hours of admission to a hospital, in the absence of hospitalization in the preceding 12 weeks is considered community-acquired. A case of CDI is classified as indeterminate if symptom onset occurs in the community between 4 and 12 weeks after discharge from a hospital (McDonald *et al* 2007, Cohen *et al* 2010). While these definitions may serve surveillance purposes, they may be limited by the complex epidemiology of CDI including the role of asymptomatic colonization (see section 1.8)

1.4 Risk Factors for C. *difficile* infection

Exposure to antibiotics is considered to be the primary risk factor for CDI. Other observed risk factors are elderly status, hospitalization, presence of clinical co-morbidities and

exposure to proton pump inhibitors and histamine 2 (h2) antagonists (Gerding *et al* 1986, McDonald *et al* 2012, Yip *et al* 2001, McCusker *et al* 2003, Gaynes *et al* 2004, Alfa *et al* 1999, Mullane *et al* 2011, Petrella *et al* 2012, Shaughnessy *et al* 2012, Deshpande *et al* 2013, Brown *et al* 2013, Evans and Safdar 2015)

The proposed mechanism by which antibiotics increase the risk of CDI is antibiotic-induced deterioration of the gut microbiota, an important barrier to C. *difficile* colonization. Spore formation confers C. *difficile* with the ability to withstand exposure to antibiotics that are harmful to the normal gut flora. Under favorable conditions however, spores germinate to toxigenic vegetative cells. Normal gut flora inhibit this process by metabolizing primary bile salts (cholate) which are essential for the germination process (Rolfe *et al*, 1981, Setlow *et al* 2003, Cloud and Kelly 2007, Giel *et al* 2010, Rineh *et al* 2014). This activity of the gut flora therefore tends to maintain C. *difficile* spores in a quiescent or dormant state. Antibiotic-induced disruption of the gut flora however, results in an increase in primary bile salts and a reduction in the level of protective secondary metabolites. Degeneration of gut microbiota is also believed to foster C. *difficile* invasiveness by providing vegetative C. *difficile* cells greater access to gut cell receptors and nutrients (n-acetyl glucosamine, sialic acid, sugars, alcohol, fructose (Rosa *et al* 2018)

Virtually all antibiotic groups are known to increase the risk of CDI although certain agents including the fluoroquinolones, cephalosporins and clindamycin, have been especially associated with increased rates of CDI in both healthcare and community

settings (Gerding 2004, Deshpande *et al* 2013, Brown *et al* 2013, Slimings and Riley 2014, Spigaglia 2016). The association between CDI and the use of one or more groups of antibiotics may differ from one setting to the next due to differences in the patterns of use of these agents. In a systematic review, Slimings and Riley (2014) observed that carbapenems and trimethoprim/sulphonamides were also associated with an increased risk of CDI in some studies, but not in others.

Cumulative antibiotic exposure also appears to be important, as evidenced by studies showing that the risk of CDI increases with duration of antibiotic treatment (Zimmerman *et al* 1991, Yee *et al* 1991, Gaynes *et al* 2004, Pepin *et al* 2005, Stevens *et al* 2011).

While antibiotic exposure is considered the primary risk factor for CDI, studies such as Dial *et al* (2008) suggest that the association between antibiotic exposure and CDI may be confounded by other CDI risk factors including hospitalization or the presence of multiple co-morbidities.

1.5 Elderly status and C. *difficile* infection

CDI studies have consistently associated the elderly with the disease (McDonald *et al* 2006, Lucado *et al* 2012, Zilberberg *et al* 2011, Tartof *et al* 2014, Khanna *et al* 2012).
In a large US study of 2.3 million discharges (Pechal *et al* 2016), CDI incidence was significantly higher among the elderly (11.6 CDI discharges/1000 total discharges), followed by adults (3.5 CDI discharges/1000 total discharges) and children (1.2 CDI discharges/1000 total discharges). The disproportionate incidence of CDI among the

elderly has been attributed to a relatively higher level of co-morbidities, hospitalization and antibiotic exposure in this age group (Owens *et al* 2008), Changes in the gut microbiota (flora) and immunosenescence are also considered to predispose the elderly to CDI.

In a molecular study in Italy, Biagi *et al* (2010) compared the gut microbiota of young adult (20-40), elderly (60-80) and centenarian (99-104) subjects. The microbiota of adult and elderly subjects were found to be similar. Deteriorative (reduced bio-diversity) changes were observed only among centenarians. Odamaki *et al* (2016) made a similar observation in Japan. This contrasts however with Wang *et al* (2015) in China in which a higher level of gut bio-diversity was observed among centenarians compared to younger subjects. In Wang *et al* (2015) a high fibre diet was also associated with an increased composition of the gut microbiota. These observations suggest that being elderly does not necessary imply an increased risk of CDI due to loss of the protective gut microbiota but that population genetics, cultural, dietary and other environmental factors may be important.

Studies have also shown that apart from the protective colonization resistance provided by the gut microbiota, the immune system also mounts a response to the presence of tCd through the production of IgG antitoxin A antibodies (Kyne *et al* 2001, Poutanen *et al* 2004, Owens 2008). Kyne *et al* (2001) observed a significantly higher likelihood of CDI recurrence among elderly patients unable to demonstrate an increase in IgG titre following their initial infection. This is suggestive of immunosenescence, a condition

associated with aging, and probably another reason for the observed link between CDI and the elderly. This may be confounded by other co-morbidities also linked with CDI, many of which are predominant in the elderly. These include dementia, congestive cardiac failure, chronic obstructive pulmonary disease, peripheral vascular disease, and psychosis (Tartof *et al* 2014, Evans and Safdar 2015).

1.6 Proton Pump Inhibitors and C. *difficile* infection

Although antibiotic exposure is considered the primary risk factor for CDI, gastric acid suppression linked to the use of h2 antagonists and proton pump inhibitors (PPIs) has also been associated with an increased risk. A number of reports have highlighted the increasing and often inappropriate use of these medications (Choudhry *et al* 2008, Rotman and Bishop 2013). Dial *et al* (2005, 2008) observed an association between the use of PPIs and community-acquired CDI. Similarly, a meta-analysis of studies from 1990 to 2010 on the use of PPIs and CDI (Janarthanan *et al* 2012) estimated that patients using PPIs had a 65% increased risk. Another meta-analysis (Kwok *et al* 2012) estimated that combined exposure to antibiotics and PPIs results in an almost doubling of CDI risk. The proposed mechanism of action of PPIs is similar to that of antibiotics, involving the disruption of colonization resistance in the gut, leading to an increase in CDI susceptibility. In a clinical trial Seto *et al* (2014) demonstrated that low and high doses of PPIs induced a decline in gut flora that was reversed upon discontinuation of PPIs.

The evidence linking H2 antagonists and PPIs with CDI remains equivocal however, as other studies have been unable to observe this association (Naggie *et al* 2011, Tleyjeh

et al 2012). In their meta-analysis, Tleyieh *et al* found the quality of studies supporting an association between the use of PPIs and CDI to be low.

1.7 Community-acquired C. *difficile* infection

Although CDI has usually been associated with elderly hospitalized patients, the disease is now increasingly seen in the community among persons with or without a recent history of hospitalization or antibiotic exposure (Dial *et al* 2008, Lambert *et al* 2009, Freeman *et al* 2010, Evans and Safdar 2015, Khanna *et al* 2012, Gupta and Khanna 2014). This includes children and younger adults (American Academy of Paediatrics 2013, Antonara and Leber 2016, Katz *et al* 2016).

In a Canadian population surveillance study Lambert *et al* (2009) observed that at least 40% of CDI cases identified had onset in the community. The authors comment that more than 75% of the community acquired CDI cases identified would have been missed by relying on a hospital-only surveillance system. It has been suggested that the increasing trend in community-acquired CDI among people who would normally be considered low risk, may be linked to increasing levels in the community of hypervirulent strains such as tCd strains such as ribotypes 027 and 078. These strains have usually been associated with healthcare settings (Goorhuis *et al* 2008, Burke and Lamont 2014)

Community-acquired CDI has also been associated with the use of chemotherapeutic agents, h2 antagonists/proton-pump inhibitors, previous hospital admission, residence in a long term care facility, and a range of co-morbidities. These co-morbidities include

inflammatory bowel disease, irritable bowel syndrome, renal failure, gastric acid suppression, low albumin, chronic kidney disease, immunodeficiency including human immunodeficiency virus (HIV) infection, hypoalbuminemia, malignant lesions and solid organ transplant (Dial *et al* 2008, Jump 2013, Gupta and Khana 2014)

1.8 Asymptomatic colonisation

The initial outcome of exposure to tCd is asymptomatic colonization. This may represent a brief or extended interlude prior to infection. Some studies have described extended periods (weeks to several months) of colonization (Furuya-Kanamori *et al* 2015, Lin *et al* 2015, Ozaki *et al* 2004, Kato *et al* 2001, Johnson *et al* 1992, Samore *et al* 1994). The factors influencing duration of a colonization are still not defined.

In a systematic review and meta-analysis, Zacharioudakis *et al* (2015) estimated that persons colonized with tCd strains are at significantly higher (x6) risk of developing symptomatic disease than non-carriers. This observation has also been made in other studies (Caroff *et al* 2017, Lin *et al* 2015, Nissle *et al* 2016, Blixt *et al* 2017, Deshpande *et al* 2015, Kagan *et al* 2017, Baron et al 2019). Since admission screening for asymptomatic colonization is not the practice in many settings, such observations may have implications for antibiotic stewardship programs employing the incidence of nosocomial CDI as a metric. A patient asymptomatically colonized at admission may present with symptoms at some point during their admission and be mis-classified as an incident case of nosocomial CDI. This assertion is consistent with the findings of Longtin

et al (2016) who observed a 62% decline in the rate of nosocomial CDI following the implementation of active surveillance for asymptomatic tCd carriage.

Additional evidence of the importance of asymptomatic carriage in CDI epidemiology is provided by studies implicating asymptomatic tCd carriage as a risk factor for the transmission of tCd in healthcare settings (Clabots *et al* 1992, Guerrero *et al* 2013, Longtin *et al* 2016, Blixt *et al* 2017, Curry *et al* 2013, Lanzas *et al* 2011, Eyre *et al* 2013 Malamou-Ladas *et al* 1983, Savage and Alford 1983, Barbut and Petit 2001).

Since asymptomatic colonization is a prelude to tissue invasion and symptomatic disease, it is not unexpected that like CDI, it has also been associated with antibiotic exposure in both healthcare and community settings (Clabots *et al* 1992, Hutin *et al* 1997, Samore *et al* 1994, Starr *et al* 2003, Ryan *et al* 2010, Donskey *et al* 2015, Ziakas *et al* 2015, Nissle *et al* 2016, Kong *et al* 2015, Furuya-Kanamori *et al* 2017).

The evidence linking asymptomatic colonization with antibiotic exposure is equivocal however, since other studies (Alasmari *et al* 2014, Loo *et al* 2011, Leekha *et al* 2013, Eyre *et a*l 2013, Behar *et al* 2017) have not made this association. In these latter studies, asymptomatic tCd colonization has been linked with the use of h2 antagonists/proton pump inhibitors, chemotherapy, previous history of CDI, malnutrition, steroid/other immunosuppressant exposure, and chronic dialysis.

Much remains to be understood on the relationship between asymptomatic tCd colonization and infection. However, the available evidence suggests a thin line between these two components of the CDAD spectrum, and highlight a potential weakness of current surveillance definitions used to distinguish nosocomial and community-acquired CDI.

1.9 Antibiotic resistance mechanisms in C. *difficile*

C. *difficile* infection is often described as an adverse outcome of antibiotic use. The pathogenesis of tCd strains is due not only to the production of tissue invasive toxins, but their ability to effectively resist a range of antibiotics. Frequent use of an antibiotic/class has been observed to select for tCd strains resistant to that antibiotic. This is particularly enhanced if the inhibitory effects of the antibiotic on tCd are minimal while causing significant deterioration of the gut microbiota.

Selection pressure appears to explain the association between CDI and clindamycin, the cephalosporins and fluoroquinolones, which coincided with the introduction and popular use of these agents. The association between clindamycin and CDI was made in the 1970's, the cephalosporins in 1980s and 90's, followed later by the fluoroquinolones (Climo *et al* 1998, McNulty *et al* 1997, Gerding *et al* 2004, Gaynes *et al* 2004, Owens *et al* 2008, Jump, 2013, Slimings and Riley 2014).

The emergence of the fluoroquinolone-resistant tCd ribotype 027 in North America, Europe and other parts of the world is believed to have been due to the widespread use

of the fluoroquinolones (Jump, 2013, Bauer *et al* 2011, Cohen *et al* 2014, Katz *et al* 2018). The resolution of CDI outbreaks associated with ribotype 027 following the withdrawal or replacement of fluoroquinolones (Gaynes *et al* 2004, Valiquette *et al* 2007, Kallen *et al* 2009, Aldeyab *et al* 2011), cephalosporins (Mcnulty *et al* 1997), and clindamycin (Climo *et al* 1998, Muto *et al* 2007) is additional evidence of the role of selection pressure, and the importance of antibiotic resistance to the epidemiology of CDI.

C. *difficile* resistance mechanisms include target site modification, increased drug efflux and inactivation, and reduced drug permeability. Alteration of the DNA gyrase target site, increased active efflux or decreased permeability appear to be the main mechanisms of resistance to the fluoroquinolones (Dridi *et al* 2002). Alteration of target ribosomes appear be the mechanism of C. *difficile* resistance to clindamycin (Leclercq, 2002). The mechanism of resistance to cephalosporins is unknown even though the majority of C. *difficile* strain have been observed to be resistant to this class of antibiotics (Huang *et al* 2009, Spigaglia 2016, Banawas 2018).

Most strains of C. *difficile* remain sensitive to first and second line agents used for treating CDI (metronidazole, rifamycins, vancomycin and fidaxomicin) However, there is some evidence of resistance and treatment failure associated with these agents as well. (Huang *et al* 2009, Spigaglia 2016, Banawas 2018). Adler *et al* (2015) reported a CDI outbreak in Israel linked to a NAP1/027 toxigenic C. *difficile* (tCd) strain with reduced susceptibility to metronidazole.

Table 1 Resistance of C. *difficile* to antibiotics used for treating CDI

Antibiotic/Class	Mechanism of action	C. *difficile* Resistance Mechanism	Reference
Metronidazole	Inhibition of bacterial DNA synthesis, DNA damage	Reduced drug activation via reduced activity of nitroreductases, reduced entry and increased efflux of the drug, increased DNA repair, increased bio-film production	Lofmark *et al* 2010, Chong *et al*. 2014; Dapa *et al* 2013,Moura *et al*. 2014, Vuotto *et al*. 2016
Rifaximin/Rifamycins	Binding with DNA dependent RNA polymerase, inhibition of DNA transcription	Mutations of RNA polymerase	Campbell *et al* 2001, Curry *et al* 2009, O'Connor *et al* 2008, Pecavar *et al* 2012
Fidaxomicin	Binding with DNA-dependent RNA polymerase, inhibition of DNA transcription	Mutations of RNA polymerase	Goldstein *et al* (2011), Leeds *et al* 2014

Rifamycin resistance rates ranging from 7.9%- 80% resistance have been observed in various global settings including Canada (Tenover *et al* 2012), Europe (Rodrıguez-Pardo *et al* 2013, Eitel *et al* 2015, Terhes *et al* 2014 and Obuch-Woszczatynski 2013), China (Huang *et al* 2010) and South Korea (Kim *et al* 2012). These variations in rifamcyin resistance may reflect differences in the use of this drug for other therapeutic purposes. Resistance mechanisms to metronidazole, rifamycins and fidaxomicin are outlined in table 1. The mechanism of resistance to vancomycin remains unclear.

1.10 Summary

Reducing the rate of CDI may well be antibiotic stewardship's lowest hanging fruit. However, the epidemiology of the disease is complex, and influenced not only by antibiotic exposure but microbial and clinical factors as well. These factors need to be taken into account when employing the rate of CDI as metric to evaluate the impact of a hospital antibiotic stewardship program. Given the reality of the care continuum, another important consideration is the extent to which antibiotic exposures beyond the hospital setting might influence the rate of CDI in the hospital.

CHAPTER 2 Literature Review

A literature search was conducted (using Embase, Web of Knowledge, Pubmed and Google Scholar) to identify studies on the impact of antibiotic stewardship interventions on CDI, antibiotic stewardship in Saudi Arabia, epidemiology of CDI in Saudi Arabia and antibiotic consumption in Saudi Arabia. Titles, abstracts and key words were searched using a combinations of terms: 'antibiotic' OR 'antimicrobial' AND 'stewardship' "Clostridium *difficile*' "diarrhea" 'impact' 'outcome' 'effect' 'prescribing' 'resistance' 'infection' 'treatment' 'over the counter' 'self-medication' 'consumption' 'self use' 'self prescribed' 'Saudi Arabia'

The truncations "diarr" and "clost" were also used. The reference list of relevant studies identified were also reviewed. The search was limited to English language resources.

2.1 Studies of antibiotic stewardship and impact on C. *difficile* Infection

Fifty five (55) primary studies were identified, describing the impact of antibiotic stewardship programs (ASPs) on CDI (appendix 1). The majority (50/55; 91%) were from North America and Europe. Studies from three countries USA, United Kingdom and Canada accounted for 76% (42/55) of the studies. The remaining 13 studies were from Australia (2), Italy (2), Saudi Arabia (2), Austria (1), Germany (1), Ireland (1), Mexico (1), Spain (1), Sweden (1) and Taiwan (1) Almost all (54/55) were hospital-based, with only one in a long term care facility.

The majority (48/55; 87%) were retrospective studies involving the comparison of the rate of CDI before and after the implementation of antibiotic stewardship. The other 7 consisted of 6 prospective studies and 1 cluster randomized trial.

34/55 (62%) studies reported a statistically significant decline in the rate of CDI following the implementation of antibiotic stewardship, while 19/55 studies were unable to observe an effect. Two studies (Khan and Cheesbrough 2003, Yam *et al* 2003) reported a reduction in the rate of CDI but did not comment on the statistical significance of their outcomes.

Formulary restriction/pre-authorization of one or more high-risk for CDI antibiotics was the stewardship intervention most strongly associated with a positive outcome. 20/24 (83%) ASPs employing this strategy observed a significant reduction in the rate of CDI (Table 2). This contrasted with programs employing prospective audit and feedback as the core stewardship intervention in which only 11 of 23 (45%) reported a significant reduction in the rate of CDI. Similarly, only 3/8 (37%) stewardship programs employing supplemental interventions alone observed a significant decline in CDI.

Table 2

CDI outcomes in ASPs employing formulary restriction/pre-authorization

Study	Outcome
Aldeyab *et al* 2012	decline in CDI incidence of 0.0047/100 bed-days per month P=.0081
Bond *et al* 2017	decline in CDI incidence of 1.2 cases/10 000 occupied bed days/month (p<.01)
Climo *et al* 1998	decline in the monthly mean number of CDI cases from 11.5 to 3.33 cases (p< .001),
Dancer *et al* 2013	77% decline in hospital acquired CDI from 2.398 to 0.549 cases/1000 patient beds
Fowler *et al* 2007	decline in CDI incidence (rate ratio 0.35 p=.009)
Gulihar *et al* 2009	decline in CDI incidence from 7.1 to 1.5% (p < .001)
Kallen *et al* 2009	22% decline in incidence of hospital-onset CDI (p=.02
Ludlam *et al* 1999	50% decline in annual CDI incidence from 98 to 45 cases
McNulty *et al* 1997	>50% decline in 7-month CDI incidence from 37 to 16 cases (p=.002).
Moffa *et al* 2018	decline in healthcare-associated CDI from 0.84 to 0.28/1000 patient days (p= 0.035).
Muto *et al* 2007	71% decline in incidence of healthcare-acquired CDI (p<.001)
Nuila *et al* 2008	42% decline in mean CDI incidence from 2.2 to 1.1 cases/1000 patient days (p<.001)
O'Connor *et al* 2004	decline in 4 month CDI incidence from 17 to 4 cases
Price *et al* 2010	increase in the rate of reduction in CDI incidence from 3% to 8% per month (p=.03)
Sarma *et al* 2015	decline in CDI (incidence rate ratio 0.332)
Shea *et al* 2017	decline monthly CDI cases from 4 to 2 cases/10,000 patient days
Stone *et al* 1998	decline in CDI incidence from 3.35 to 1.94 per 100 admissions (p<0.05)
Talpaert *et al* 2011	decline in CDI (incidence rate ratio 0.34) P<0.0001
Thomas *et al* 2002	decline in CDI incidence from 2.09 to 0.87 cases per 1000 discharges (P<.0001)
Wenisch et al 2014	46% reduction in mean number of CDI cases per month (P<0.0044)

These findings are consistent with Feazel *et al* (2014) who in their systematic review observed that programs employing formulary restriction and pre-authorization had the most impact on CDI reduction. Interestingly this observation conflicts with two studies in the current review (Jenkins *et al* 2015, Giacobbe *et al* 2017). Although both studies employed both prospective audit/feedback and formulary restriction/pre-authorization,

neither observed a significant reduction in the rate of CDI. Similarly, Patton *et al* (2017) in their review identified only 2 out of six studies observing a significant association between restriction of high risk antibiotics and a reduction in CDI. These discrepancies may be attributable to differences in study design and/or population as well as other context-specific outcome determinants.

In line with this, it is interesting that ASPs specifically targeting the elderly, or employing a "bundled" approach of antibiotic stewardship, infection control and hand hygiene interventions, were associated with a significant impact on CDI (Tables 3 and 4 respectively).

Table 3 CDI outcomes in programs targeting the elderly

Study	Outcome	Primary stewardship intervention
Beaulac *et al* 2016	decline in CDI incidence (rate ratio 0.57 p=.02)	Prospective audit and feedback
Fowler *et al* 2007	decline in CDI incidence (rate ratio 0.35 p=.009)	Formulary restriction
Gulihar *et al* 2009	decline in CDI incidence from 7.1 to 1.5% (p < .001)	Formulary restriction
Jump *et al* 2012	increased rate of decline in C. *difficile* positivity (p=.04)	Prospective audit and feedback
Ludlam *et al* 1999	50% decline in annual CDI incidence from 98 to 45 cases	Formulary restriction
McNulty *et al* 1997	>50% decline in 7-month CDI incidence from 37 to 16 cases (p=.002).	Formulary restriction
O'Connor *et al* 2004	decline in 4 month CDI incidence from 17 to 4 cases	Formulary restriction
Starks *et al* 2008	decline in 2-year CDI incidence from thirty-eight to 14 cases (4.2 to 1.6%,p=.009)	None (supplemental)
Stone *et al* 1998	decline in CDI incidence from 3.35 to 1.94 per 100 admissions (p<0.05)	Formulary restriction

9/9 (100%) studies of ASP specifically targeting the elderly reported a significant reduction in the rate of CDI.

Similarly, a significant reduction in the rate of CDI was observed in 9/9 (100%) studies of bundled programs (Table 4). Notably, formulary restriction/preauthorization was the core stewardship intervention predominantly employed in both these groups of studies.

Table 4 CDI outcomes in "bundled" programs

Study	Outcome	Primary stewardship intervention
Cook and Gooch 2015	42.6% decline in the incidence of nosocomial CDI (p = 0.005)	Prospective audit and feedback
Climo *et al* 1998	decline in the monthly mean number of CDI cases from 11.5 to 3.33 cases (p< .001),	Formulary restriction
Gulihar *et al* 2009	decline in CDI incidence from 7.1 to 1.5% (p < .001).	Formulary restriction
Kallen *et al* 2009	22% decline in incidence of hospital-onset CDI (p=.02)	Formulary restriction
McNulty *et al* 1997	>50% decline in 7-month CDI incidence from 37 to 16 cases (p=.002).	Formulary restriction
Muto *et al* 2007	71% decline in incidence of healthcare-acquired CDI (p<.001)	Formulary restriction
Price *et al* 2010	significant increase in the rate of reduction in CDI incidence from 3% to 8% per month (p=.03)	Formulary restriction
Stone *et al* 1998	decline in CDI incidence from 3.35 to 1.94 per 100 admissions (p<0.05)	Formulary restriction
Valiquette *et al* 2007	60% decline in the incidence of nosocomial CDI (p<-007)	Prospective audit and feedback

Only 33/55 studies described the method used to detect tCd (table 5). Enzyme immuno assay (EIA) for C. *difficile* toxins A and B was most commonly employed (22/33 studies), either alone own or as part of a two or three step procedure involving EIA for C. *difficile* Glutamate dehydrogenase (GDH) antigen, and a confirmatory molecular (nucleic acid amplification) test. Cell culture cytotoxin neutralization assay (CCA) was employed in 9/33 studies either alone or as part of a two-step procedure involving a confirmatory nucleic acid amplification test (PCR). PCR was used exclusively in 2/33 studies.

Table 5 Inter-study variations in tCd test methods

Study	C. *difficile* test method	Outcome
Aldeyab *et al* 2012	EIA-toxins A/B	decline in CDI incidence
Bond *et al* 2017	EIA-GDH; :toxins A/B; PCR confirmation of discordant result	decline in monthly CDI incidence
Borde *et al* 2015	GDH;EIA	no significant impact
Carling et al 2003	cell culture-cytotoxin assay	decline in CDAD incidence
Chan *et al* 2011	culture (type not specified)	no significant impact
Climo *et al* 1998	cell culture-cytotoxin assay	decline in monthly CDI incidence
Cook and Gooch (2015	EIA-GDH;A/B, Cell culture-cytotoxin assay, NAAT	decline in CDI incidence
Cook *et al* 2011	cell culture-cytotoxin assay	no significant impact
Cruz-Rodriguez *et al* 2014	EIA-toxins A/B	no significant impact
Dancer *et al* 2013	EIA-toxins A/B	decline in CDI incidence
Giacobbe *et al* 2017	EIA-toxins A/B;GDH	no significant impact
Gulihar *et al* 2009	EIA-toxins A/B	decline in CDI incidence
Jenkins *et al* 2015	EIA-GDH,toxins A/B; PCR	no significant impact
Kallen *et al* 2009	EIA-toxins A/B	decline in hospital onset CDI incidence
Kandel *et al* 2016	EIA-toxins A/B, PCR	no significant impact
Khan and Cheesbrough 2003	cell culture-cytotoxin assay	decline in nosocomial CDI
Ludlam *et al* 1999	cell culture-cytotoxin assay	decline in CDI incidence
McNulty *et al* 1997	cell culture-cytotoxin assay-	decline in CDI incidence
Moffa *et al* 2018	PCR	decline in healthcare-associated CDI incidence
Muto *et al* 2007	cell culture-cytotoxin assay	decline in CDI incidence
Nuila *et al* 2008	EIA-toxins A/B	decline in CDI incidence
O'Connor *et al* 2004	EIA-toxins A/B	decline in CDI incidence
Patton *et al* 2017	EIA-toxins A/B;GDH	no significant impact
Price *et al* 2010	EIA-toxins A/B	change in rate of decline in nosocomial CDI incidence
Sarma *et al* 2015	EIA-toxins A/B	decline in hospital-acquired CDI incidence
Schon *et al* 2011	EIA-toxins A/B	no significant impact
Shea *et al* 2017	PCR	decline in mean monthly CDI incidence
Stone *et al* 1998	EIA-toxin A	decline in CDI incidence
Storey *et al* 2012	EIA-toxin A/B; PCR	no significant impact
Talpaert *et al* 2011	EIA toxin A/B	decline in CDI incidence
Tedeschi *et al* 2017	EIA toxin A/B; GDH	decline in CDI incidence
Thomas *et al* 2002	cell culture-cytotoxin assay	decline in CDI incidence
Wenisch *et al* 2014	PCR; EIA GDH	decline in nosocomial CDI incidence

Among the non-molecular tests, cytotoxigenic culture is considered the most sensitive, followed by CCA, and the two-step method of EIA for GDH and toxins A/B. EIA testing for toxin A/B alone is considered to be the least sensitive (Barbut *et al* 1993, Peterson *et al* 2007, Eastwood *et al* 2009, Longtin *et al* 2013).

The sensitivity of nucleic acid amplification tests (NAAT) such as PCR significantly surpass most non-molecular methods. In a comparative study, Longtin *et al* (2013) estimated that direct PCR testing of stool rather than a three-step protocol of EIA for GDH, EIA for toxins A/B followed by CCA resulted in a 50% increase in CDI incidence. Other comparative studies also illustrate the relatively low sensitivity of EIA compared with other methods. Peterson et al (2007) and Eastwood et al (2009) observed EIA sensitivities of 73.3 and 75% respectively (Table 6). Studies employing EIA alone are therefore at greater risk of false negative tCd results, and are more likely to under-estimate the rate of CDI. On the other hand reliance on highly sensitive molecular tests alone may increase the likelihood of over-estimating the rate of CDI (false positives), especially if unaccompanied by clinical diagnostic criteria.

Table 6 Comparative studies of tCd test methods

Study	Test	Sensitivity (%)	Specificity (%)
Peterson *et al* 2007	cytotoxigenic culture	100	95.9
	RT PCR	93.3	97.4
	CCA	76.7	97.1
	EIA	73.3	97.6
Eastwood *et al* 2009	PCR	88.5**	95.4
	EIA	75**	96.1

**compared to cytotoxigenic culture

These differences in the sensitivity of tCd test methods are likely to bias comparisons of antibiotic stewardship studies on the basis of CDI outcome (Longtin *et al* 2013, Kamboj *et al* 2018). Changes from a less to a more sensitive tCd test method may also hinder intra-study comparison as reported by Storey *et al* (2012), Jenkins *et al* (2015), Cook and Gooch (2015) and Moffa *et al* 2018).

The duration of stewardship interventions appeared unrelated to CDI outcome. The mean duration of interventions was 2.1 years (range 0.5 to 6.25 years). Interventions associated with a significant decline in the rate of CDI following stewardship implementation did not differ in terms of duration from those not observing an effect, with mean durations of 2.1 and 1.9 years respectively.

Only 17/55 (27%) studies reported the level of prescriber compliance with stewardship. Acceptance of stewardship recommendations ranged from 75-99%. No correlation was observed however between the reported stewardship acceptance rate and CDI outcome (data not shown).

Although the gold standard, randomized trials are challenging to implement in antibiotic stewardship. This is due to pre-existing evidence of the benefits of judicious antibiotic prescribing, and the difficulties overcoming the inevitable ethical constraints. One way around this is the stepped-wedge design. This was employed in the only randomized study identified in this review (Palmay *et al* 2014). In this study non-intensive care hospital services were grouped into clusters and each cluster randomly allocated a date for the

implementation of the program which consisted of prescriber education and prospective audit and feedback. Following the antibiotic stewardship intervention, the rate of CDI in each service was compared to the rate in a six month period during which none of the services received stewardship. The program was not associated with a significant decline in the rate of CDI however. The authors attribute this outcome to the inability of the stewardship program to influence the use of the targeted broad spectrum antibiotics. Notably, formulary restriction was not among the interventions. It is plausible that if implemented, it may have changed the study outcome.

The CDI metric employed in most of the studies reviewed (52/55; 95%) was the incidence of nosocomial CDI standardized per 1000 or 10000 patient days.
The problem with this metric however is that it only measures the impact of antibiotic stewardship on preventing new cases of CDI. Given the complex epidemiology of CDI, this metric appears somewhat simplistic. Due to its specificity, it is unable to measure the impact of the stewardship program on the rate of CDI recurrence, or CDI among specific high-risk groups such as the elderly and immunocompromised.

A number of studies (Drekojna *et al* 2011, Shaughnessy *et al* 2012, Deshpande *et al* 2015, Watson and Graber 2018, Chia *et al* 2019) have associated exposure to non-CDI antibiotics with an increased risk of CDI recurrence. Watson and Graber (2018) also observed that prescribing practices seemed unaffected by prescribers' knowledge of a patients' recent CDI history.

Chia *et al* (2019) observed a significantly lower rate of CDI recurrence among patients managed by physicians accepting stewardship recommendations compared with patients whose physicians were non-compliant. These studies support the assertion that preventing CDI recurrence among high risk patients is an important antibiotic stewardship performance indicator that may not be captured in measuring the incidence of nosocomial CDI alone.

It may be that the preponderance of nosocomial CDI incidence as a metric in antibiotic stewardship studies is driven by other considerations, among which may be mandatory public reporting of healthcare-asociated infections (HAI). The majority of antibiotic stewardship studies emerge from geographical settings where public reporting of HAI by hospitals and other facilities is mandatory (North America and Europe). In the US, apart from being reported to the National Healthcare surveillance network (NHSN), data on CDI and other HAI incidence is collected by Medicare and used to evaluate hospital performance. This has financial implications in terms of reimbursements to a given hospital (Mcdonald et al 2012). Perhaps in light of this expectation, the potential risk of reputation or finanacial loss, and a high prevalence community CDI prevaence, reducing the incidence of nosocomial CDI takes priority. This may explain why the impact of antibiotic stewardship is frequently evaluated with respect to this particular metric.

The findings of this review suggest that the impact of antibiotic stewardship on the rate of CDI varies from one setting to the next, and is likely influenced by the interaction of several determinants (study population, type of intervention, laboratory diagnostic method), a number of which may be context specific. Stewardship program

characteristics observed to correlate most with a significant reduction in the rate of CDI were targeting of the elderly, formulary restriction and pre-authorization of high CDI risk antibiotics, and bundling of antibiotic stewardship, infection control and hand hygiene interventions. Overall, 34/55 (62%) studies reported a statistically significant decline in the rate of CDI following the implementation of antibiotic stewardship. In other reviews 52% (Feazel *et al* 2014), 32% (Baur *et al* 2017) and 48% (Davey *et al* 2017) of studies associated antibiotic stewardship with a reduction in the rate of CDI.

Additional details of the 55 studies reviewed may be found in appendix 1.

2.2 Antibiotic Stewardship studies in Saudi Arabia

The review identified twelve studies of antibiotic stewardship interventions in Saudi Arabia (appendix 2). In the majority (11/12, 92%) the primary metrics were impact of stewardship on prescribing processes, antibiotic consumption and associated costs. Three studies reported microbial outcomes, two of which included the rate of CDI (Al-Tawfiq *et al* 2015 and Amer *et al* 2013). Only Al-Tawfiq *et al* observed a significant decline in the incidence of CDI following the implementation of restricted reporting of antibiotic susceptibilities. In this study however, reducing the rate of CDI was not an explicit outcome of interest. Amer *et al* (2013) did not observe an impact of their intervention on the rate of CDI.

2.3 Prescriber practices and perceptions of antibiotic stewardship in Saudi Arabia

Studies on prescribing practices and prescriber perceptions of antibiotic guideline in Saudi Arabia, suggest similar motivations between Saudi prescribers and those in other global settings (section 1.1.). In a survey of physicians at two tertiary care centres

(Alothman *et al* 2015), opinions were split, with half of the physicians disagreeing with antibiotic restriction as an intervention to improve prescribing practices and reduce microbial resistance. Education was the preferred method of engagement. This preference for education as a stewardship intervention rather than antibiotic restriction was also highlighted in another survey of physicians across four tertiary care centres in Eastern Saudi Arabia (Baadani *et al* 2015). In both studies only a minority of physicians considered antibiotic guidelines useful. None of the studies cited explored the rationale for physical preference for education, and opposition to prescribing guidelines and formulary restriction/pre-authorization. It may be that among the various stewardship interventions, antibiotic-related education is preferably the least threatening in terms of physician autonomy.

Al-Harthi *et al* (2015), found patients' or family expectations or demand for antibiotics to significantly influence antibiotic prescribing practice. Salahuddin *et al* (2016) observed that while physicians may be aware of guidelines for de-escalating a patient from a broad to narrower spectrum antibiotic regime, they were apprehensive about making this decision themselves. Reluctance to de-escalate was most commonly observed in the management of patients considered to have a high risk of clinical complications. In the absence of an infectious disease physician or pharmacist, maintaining broad spectrum coverage appeared to be the safest option. Reluctance to de-escalate from broad to narrow spectrum antibiotics was also observed by Youssif *et al* in (2018) in a study on peri-operative antibiotic prophylaxis.

Similar observations have been made among dentists, another group of antibiotic prescribers.

In a cross-sectional survey (Al-Harthi *et al* 2013), the majority of dentists in Jeddah Saudi Arabia acknowledged that inappropriate use of antibiotics was common in the profession. For a significant proportion of respondents however, the choice of antibiotic appeared to be driven primarily by availability rather than the cause/indication of disease. Lack of acceptance or respect for institutional antibiotic use guidelines was also observed. Amoxycillin-clavulanate (broad spectrum) was the most commonly prescribed, although the dose and duration of treatment varied. Prescribing antibiotics was observed by Al-Harthi *et al* (2013) to be a means by which dentists gained re-assurance and peace of mind, especially in situations of high patient load.

In another survey of dentists in Jeddah, Al-Sebaei and Jan (2016), report that the majority (77%), contrary to guidelines, would prescribe antibiotics following routine dental extraction. While most respondents agreed that this practice may be associated with increase in bacterial resistance in the community, it was still perceived as necessary for preventing infections. In another survey of 195 dentists in three regions of southern Saudi Arabia (Najran, Gizan and Asser), Alattas and Alyami (2017) report that contrary to dental guidelines, 8.1 to 28.1% of dentists would prescribe antibiotics for endodontic conditions not requiring antibiotics. Al-Johani *et al* (126 dentists surveyed) in Western Saudi Arabia also identified Amoxicillin-clavulanate as the most commonly prescribed antibiotic (73.8%), and also report a low level of compliance (9.5 to 45%) with antibiotic guidelines. Others studies in Northern and Western Saudi Arabia (Iqbal, 2015 and AlRahabi and

Abuong, 2017 respectfully) have also highlighted inappropriate use of antibiotics in the management of endodontic conditions. These findings suggest that, as observed in other settings, perceived loss of autonomy and emotion-driven (fear of not providing sufficient antibiotic coverage) prescribing may pose barriers to compliance with antibiotic stewardship interventions in Saudi Arabia.

2.4. Epidemiology of C. *difficile* infection in Saudi Arabia

Most of what is currently known about CDI has emerged from studies in North America and Europe. To date the number of epidemiological studies on CDI from other parts of the world, particularly Asia, the Middle East and Africa, are relatively few. A systematic review of 48 studies on CDI in South/East Asia and the Middle East (Borren *et al* 2017) yielded a pooled CDI prevalence of 14.8% (16.4% among hospitalized patients with diarrhea). Another review of CDI prevalence in low and middle income countries in Asia, South America and Africa (Roldan *et al* (2018) reported a prevalence range of 8.3-27.9% Notably, these rates are consistent with CDI positivity rates reported in European (Bauer *et al* 2011; 4-39%), and North American (Cohen *et al* 2014 6.9-20.4%;) studies. Inter-regional differences in ribotype may exist however. Collins *et al* (2013) found ribotypes 027 and 078, responsible for much of the upsurge in CDI incidence in North America and Europe to be rare in Asia. The most prevalent toxigenic ribotypes identified their study were 017, 018, 014, 002, and 001. Ribotypes 017 and 018 have been associated with extensive disease across several Asian countries. These studies suggest that the limited data on CDI from global settings other than Europe or North America are not indicative of a significant difference in the burden of CDI. It is likely that CDI is also prevalent but under-

diagnosed in many parts of the world, probably associated with C. *difficile* riboytpes that have similar potential for extensive morbidity and mortality as the NAP1/027 and 078 ribotypes in North America and Europe.

None of the ten Middle East CDI studies reviewed by Borren *et al* (2017) were from Saudi Arabia, and to date few Saudi studies on CDI epidemiology have emerged. One of these (Akhter *et al* 1994) identified C *difficile* toxin in 9.5% of gastroenteritis stools tested at a referral centre. Another study at a general medical hospital (Al-Tawfiq and Abed 2010) reported a CDI prevalence of 4.6%. Alzaharani and Al Johani (2013) conducted a case study of four patients identified with the hyper-virulent NAP1/BI/027 C. *difficile* strain) and suggest that this strain is probably prevalent but overlooked due to the absence in many Saudi hospitals of molecular technology required for identification. Similarly, Alqumber *et al* (2014) report that five out of 12 C. *difficile* isolates from samples taken from supermarket surfaces (retail baskets, trolleys, conveyor belts and plastic basins) in Saudi Arabia were identified as ribotype 027. Hudhaih and Elhadi (2019) report a tCd prevalence of 18.7% among patients with irritable bowel disease in 4 hospitals in the Eastern province of Saudi Arabia. Four ribotypes were identified including 027.

The preceding supports the assertion of Alzaharani and Al Johani (2013), that a high prevalence of toxigenic C. *difficile* strains exists in Saudi communities, underestimated perhaps by surveillance (laboratory, clinical diagnostic) limitations.

Interestingly similar CDI risk factors to those identified in European and American studies have also been identified in Saudi Arabia. In Balkhy *et al* (2019), CDI was associated with

age (elderly), immunosuppression, malnutrition, cancer chemotherapy, number and duration of antibiotics used. Otaibi *et al* (2017) observed an association between CDI and the use of Omeprazole (a proton pump inhibitor). Proton pump inhibitors were ranked third in a study of the top ten medications used in Saudi Arabia (Alkhamees et al 2018)

2.5 Antibiotic consumption in Saudi Arabia

A study of the top ten used medications in Saudi Arabia (Alkhamees *et al* 2018) ranked antibiotics and proton pump inhibitors in second and third place respectively. This report is not unexpected and is consistent with global antibiotic consumption studies such as Van Boeckel *et al* (2014) who observed an increasing trend in antibiotic consumption in Saudi Arabia from 1.5 to 2.6 dose standard units (single dose units such as a pill, capsule or ampoule) per person between 2001 and 2010. Klein *et al* (2018) also observed an increase in antibiotic consumption of 10 to 15 defined daily doses (DDD) per 1000 inhabitants per day from 2000 to 2015.

The fact that both studies observed an upward trend in Saudi Arabia is consistent with the reality of non-regulation of antibiotic use in the country. Since the observed figures are based on pharmaceutical sales data they may even be an under-estimate of the actual level of antibiotic consumption in the country. They are unlikely to reflect informal sources of antibiotic procurement in Saudi Arabia including the internet (El-Zowalaty *et al* 2016) or purchases in neighbouring Middle East countries where antibiotic consumption is also unregulated.

2.6 Self-medication with antibiotics in Saudi Arabia

The practice of SMA has been observed to account for 19-100% of antibiotic use outside North America and Northern Europe (Morgan *et al* 2011, Padget *et al* 2016) and may be indicative of non-judicious use of antibiotics in a given setting. Studies conducted among pharmacists and members of the general public suggest that SMA is common in the Middle East including Saudi Arabia. A systematic review of 22 studies from 11 Middle East countries including Saudi Arabia (Alhomoud et al 2017) reported a SMA prevalence ranging from 19% to 82%.

Studies conducted among pharmacists indicate that SMA in Saudi Arabia is not due to the absence of regulations prohibiting non-prescription sales of antibiotics, but is facilitated by public expectation, the perceptions of pharmacists themselves and a lack of government enforcement of the existing law. Al-Ghamdi *et al* (2001) conducted a study of 88 community pharmacies in the Eastern province of Saudi Arabia. Each pharmacy was presented with a patient (played by an actor) seeking treatment for a urinary tract infection. All but one pharmacist agreed to treat this patient with either a fluoroquinolone (most commonly suggested), penicillins, cephalosporins, tetracylines or co-trimoxazole. Similar observations were made by Al-Mohammadi *et al* (2013) in Jeddah (Western province). Voluntary workers posing as customers attempted to purchase antibiotics (co-amoxiclav and the second generation cephalosporin cefaclor, and other prescription-only medications. The majority of volunteers (70%) requested the medication by name while others described their symptoms and asked the pharmacist to recommend treatment.

Almost all (97.9%) the pharmacists were observed to have dispensed the requested antibiotics without requiring a prescription.

Alshammari *et al* (2017) conducted a study of 150 randomly selected community pharmacies across 6 regions in Saudi Arabia. As in previous studies voluntary workers were recruited to pose as members of the public attempting to purchase ciprofloxacin or other prescription-only medications. In 57% of encounters, pharmacies were non-compliant with the law and were willing to sell ciprofloxacin without a prescription. For comparison, the same approach was applied to government hospital pharmacy practices. Alshammari *et al* (2017) report 100% compliance (non-dispensation of ciprofloxacin without a prescription) in these settings.

In Madina (Western Saudi Arabia), Bahnassi (2016) conducted semi-structured interviews of 150 community pharmacists. Non-prescription dispensing of antibiotics was observed to be related to self-confidence among pharmacists in making diagnoses and administering treatment. Thirty six per cent (36%) of pharmacists also indicated that diarrhea was the most common adverse reactions to antibiotics reported. Thirty three per cent (33%) would recommend stopping the antibiotic when an adverse event occurs. Notably 12% indicated that they would recommend an alternative antibiotic. The most common antibiotics dispensed were amoxicillin, amoxicillin clavulanate and azithromycin. Fifty seven percent (57%) of respondents indicated their non-involvement in the choice of antibiotics selected, suggesting that specific antibiotics were requested by the customers themselves. The majority of pharmacists (82%) did not consider non-

prescription dispensing a problem and many (58%) deemed it a requirement due to limited access of the public to a physician. The most common suggestion offered to limit non-prescription antibiotic use was for health authorities to enforce regulations. Some suggested public education on antibiotic use.

In another study of 155 community pharmacists (Abujeisha and Ahmed 2018), more than 90% of the respondents indicated that cold and flu, sore throat and pharyngitis, gastroenteritis, dental pain and earache were common reasons for non-prescription dispensing of antibiotics. The majority of pharmacists identified oral penicillin, cephalosporin, macrolides, quinolones and tetracycline as commonly dispensed antibiotics. Similar to Bahnassi (2016), pharmacists interviewed in Abujeisha and Ahmed (2018) also felt they were responding to a public need, and expressed confidence in their ability to dispense antibiotics appropriately. The findings of these studies are consistent and identify pharmacists as enablers of SMA in Saudi Arabia.

The second group of SMA studies identified sought to explore the rationale for SMA among members of the public (appendix 3). Interestingly the responses from these studies are consistent with those of pharmacists. In almost all (15/18) the studies, respondents confirmed pharmacists to be the source of their non-prescription antibiotics. The most common reason cited for SMA was to treat a cold or other respiratory infection. Long waiting times to see a physician, or the illness not considered severe enough to warrant a formal health care visit were offered as reasons for SMA Notably, among the antibiotics commonly consumed by people practicing SMA were broad spectrum agents

including those considered to be high risk for CDI (cephalosporins, fluoroquinolones, clindamycin and amoxicillin-clavulanate).

Chapter 3 Study Rationale, Aim and Objectives

3.1 Study rationale

The ability of a hospital antibiotic stewardship program to reduce the burden of CDI in the hospital is an important measure of its value in increasing patient safety and reducing adverse outcomes of antibiotic use. Epidemiological studies from Saudi Arabia and other parts of the Middle East, although relatively few, suggest that CDI is common in this region. There are relatively few studies on antibiotic stewardship in Saudi Arabia and in the majority, the outcomes measured have been changes in antibiotic utilization, prescribing processes, and antibiotic expense. Studies including the rate of CDI as an outcome are sparse.

The incidence of nosocomial (healthcare acquired) CDI is the metric most commonly used in the antibiotic stewardship literature to evaluate the impact of interventions on CDI. This metric is somewhat limited however since it only measures the impact of antibiotic stewardship on preventing new cases of CDI, rather than reducing the overall burden of CDI in the hospital. Due to its specificity, it is unable to measure the impact of the program on other performance indicators including the rate of CDI recurrence, and CDI among specific high-risk groups such as the elderly and immunocompromised.

Furthermore, the incidence of nosocomial CDI is a time consuming metric that requires surveillance resources to review patient records in order to determine the date of symptom onset and categorize CDI as either healthcare, community or indeterminate source-acquired. This may often require post-discharge follow up either with the patient

or family, other healthcare facilities (that the patient may be transferred to or admitted from) and primary healthcare providers. Such resources are unavailable in many global settings including the Middle East.

The prevalence of toxigenic C. *difficile* in unformed/diarrhea stool specimens obtained from hospitalized patients offers a simpler yet more sensitive and robust metric for estimating the impact of antibiotic stewardship on the burden of tCd in the hospital. It can used to approximate CDI prevalence by testing for tCd only in unformed or diarrhea stool. Laboratory-based CDI surveillance is not without precedent, and the current US national healthcare network (NHSN) surveillance definition for nosocomial CDI is a tCd positive unformed stool specimen obtained 3 or more days after patient admission (NHSN, 2019)

As a metric, tCd prevalence lacks the specificity of nosocomial CDI incidence since it does not distinguish between community-acquired and nosocomial CDI. However it can be used to monitor secular trends and the effectiveness of antibiotic stewardship interventions in reducing the hospital CDI burden in the long term.

Despite these advantages, the utility of tCd as a metric of antibiotic stewardship is largely untested. It is also unclear whether a hospital antibiotic stewardship program could have a discernible impact on tCd prevalence in a setting with a high community prevalence of tCd and CDI risk factors such as unregulated antibiotic exposure.

3.2 Aim and Objectives

The aim of the study was to assess the impact of antibiotic stewardship on the prevalence of toxigenic C. *difficile* (tCd) among inpatients at the Dhahran health centre in Saudi Arabia, a 380-bed acute care hospital.

The study assumed a high tCd prevalence in Saudi communities related to unregulated (self-medication) exposure to antibiotics. Another assumption was that a significant proportion of patients are admitted to the study hospital asymptomatically colonized with tCd. Colonized patients are at risk of developing CDI in the hospital and may transmit tCd to other patients who may then go on to develop CDI. Given these considerations, it was hypothesised that antibiotic stewardship would not have a discernible impact on the prevalence of tCd (and CDI) in the hospital. An observation contrary to this hypothesis would be instructive, and lend support to the utility of tCd prevalence as a metric of antibiotic stewardship in the study setting.

The objectives were to retrospectively identify all in-patients tested for tCd over the study period (2005-16), and compare tCd prevalence in the six years preceding (2005-10) and six years following (2011-16) the introduction of the ASP. The findings were contrasted with those of other studies that have predominantly utilized the incidence of nosocomial CDI as the ASP metric of choice.

It was envisaged that regardless of outcome, this would be a useful addition to the few studies on antibiotic stewardship and CDI epidemiology from this region. It would also add to the body of knowledge on patient-level metrics of antibiotic stewardship, including the relevance of health care context. The study would benefit the hospital by informing CDI surveillance policy and initiatives to improve the stewardship program. Study limitations would also offer useful insights for future research.

Chapter 4: Methods

4.1 Setting

The study was conducted at the Dhahran health centre (DHC) of Johns Hopkins Aramco Healthcare (JHAH). Johns Hopkins Aramco Healthcare (JHAH) is a 5-site healthcare facility in the Eastern province of Saudi Arabia. DHC is the largest hospital of JHAH. Services include general medicine and surgery, intensive care, and management of haematological and solid organ malignancies. The hospital serves a catchment population of approximately 370,000 patients.

An antibiotic stewardship program was formally implemented in the hospital in 2011. This was against a backdrop of two previous interventions that were directly related to reducing inappropriate antibiotic use in the hospital

One of these was the service of an infectious diseases (ID) consultant. A total of 1444 infectious disease consultation requests were recorded during the 4-year period 2006-2009. Antibiotic therapy was changed in 58.7% and discontinued in 14.7% of cases after ID consultation. Interestingly CDI was the infection most commonly associated with a change in antibiotics (94.7% of consultations) (Al-Tawfiq, 2013)

The other antibiotic stewardship-related intervention that preceded the formal launch of the ASP was the introduction in 2010 of restricted laboratory reporting of antibiotic susceptibilities for selected Gram negative organisms. Susceptibility of enteric bacteria to a number of agents (amikacin, ampicillin, cefazolin, cefepime, cefuroxime, and piperacillin-tazobactam) was suppressed in laboratory reports. However, susceptibilities to some agents (aztreonam, ceftazidime, tobramycin, chloramphenicol, tetracycline,

metronidazole, and piperacillin) were released on special request by the attending physician Similarly, susceptibility of Pseudomonas aeruginosa (P. aeruginosa) isolates to amikacin, cefepime, levofloxacin, tobramycin was suppressed. For multi-drug resistant P. aeruginosa, susceptibility of isolates to aztreonam, mezlocillin and piperaciilin was also withheld from laboratory reports. The rationale for restricted reporting was to reduce inappropriate prescribing especially of broad spectrum agents. These agents were targeted on the basis on their spectrum of activity, popularity or potential for the over-prescribing, and association with adverse outcomes including microbial resistance, as well as cost (Al Tawfiq *et al* 2015).

The antibiotic stewardship program was formally implemented in 2011 starting with education sessions specifically targeted at prescribers and hospital pharmacists (Table 7). Education sessions were delivered as lectures, grand rounds on judicious antibiotic use and academic detailing in which baseline knowledge of the different antibiotics was explored, and feedback provided. This intervention was facilitated primarily by the infectious disease physician assigned to the ASP.

The other program components were introduced more or less simultaneously in 2012. These were automatic renal dosing, vancomycin pharmacokinetic monitoring to decrease adverse renal events, antibiotic de-escalation protocol, intravenous to oral conversion program, pre-operative antibiotic protocols using adapted orders, and interventions in paediatric outpatient clinics to improve treatment of upper respiratory tract infections.

Automatic renal dosing and vancomycin pharmacokinetic monitoring were led primarily by the ASP-assigned pharmacist. Antibiotic treatment was tailored to a patient's clinical profile, infecting organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the antibiotic. The rationale for these interventions is to optimise dosage and reduce the likelihood of microbial resistance particularly among patients receiving intravenous treatment. These interventions have been associated with a reduction in the total duration of antibiotic exposure and associated adverse outcomes including CDI. The drawback to dose optimization strategies however, is that they may occasionally necessitate prolonged infusion, which may conflict with other clinical needs of the patients (Septimus *et al* 2011). Details of these intervention are contained in separate report (Momattin *et al* 2015)

Conversion of intravenous to oral antibiotic administration is recognized as an important ASP strategy that has the potential to reduce the length of hospitalization and unnecessary intravenous catheterization, both of which increase the risk of infection and prolonged antibiotic exposure. This intervention involved the identification by the ASP team (ID physician and pharmacist) of patients receiving intravenous antibiotic treatment, and making recommendations as appropriate. However, reaching clinical consensus is often a challenge with this intervention. Compliance with this intervention was likely reliant on the leadership and influence of the ID physician.

The rationale for the inclusion of antibiotic de-escalation as a component of the ASP was to reduce unnecessary empiric use of broad spectrum antibiotics, and by so doing limit

adverse events and usage costs. The challenge often encountered with this particular strategy is prescriber reluctance to de-escalate from empiric therapy even when culture results are negative or alternative narrower spectrum options are available, and the patient has improved clinically (Septimus and Owens, 2011). The reassurance offered to prescribers by the use of broad spectrum antibiotics has been previously described (see section 2.3) As with intravenous to oral conversion, prescriber compliance with de-escalation was likely reliant on the input of the ID physician in terms of education and guidance to allay concerns regarding patient welfare.

The use of adapted orders for peri-operative prophylaxis was implemented as an ASP strategy as a way of streamlining prescribing practices. This strategy has been shown to improve the appropriateness of antibiotic use in surgical services (Septimus 2011). One drawback however is that the effectiveness of this intervention may be limited by automatic stop orders dictated on the ordering form, which may conflict with the patient's clinical need. This may result in prescriber non-compliance with the specifications of the adapted order.

Although primarily in-patient focused, the ASP was implemented in one outpatient service. Multifaceted interventions (rapid streptococcal antigen test, educational grand rounds, individual and group monitoring and feedback, small group discussions, questions and answers on appropriate antibiotic use, and academic detailing) were implemented in paediatric outpatient clinics to improve antibiotic prescribing practices

related to upper respiratory tract infections in children. Additional details of this intervention are contained in a previous report (Al-Tawfiq and Alawami, 2017)

The preceding indicates that between 2011 and 2016, the JHAH ASP program comprised mostly “supplemental” interventions, as described by the infectious disease society of America (Dellit *et al* 2007; see section 1.1). An internal review of the program in 2014, three years after its implementation highlighted the absence of key ASP resources (the program was supported only by one infectious disease physician with antibiotic stewardship only as part of his portfolio, and a part-time pharmacist) that would normally be required for a more robust program. The supplemental nature of the program was likely related to this resource limitation.

Table 7 JHAH Antibiotic Stewardship Interventions

Intervention	Date of Implementation
Restricted reporting of antibiotic susceptibilities**	2010
Prescriber and Pharmacist Education sessions	2011
Automatic Renal Dosing	2012
Antibiotic De-escalation protocol	2012
Intravenous to Oral Conversion Program;	2012
Vancomycin Pharmacokinetic monitoring	2012
Peri-operative antibiotic protocols using adapted orders	2012
Multiple Interventions in paediatric outpatient clinics to improve the use of antibiotics in upper respiratory tract infections	2012

** Introduced before the formal launch of the antibiotic stewardship program

4.2 Study Design

This was a quasi-experimental (non-randomized), laboratory-based retrospective study, comparing the period prevalence of toxigenic Clostridioides *difficile* (tCd) among in-patients presenting with unformed stool/diarrhea and tested at Johns Hopkins Aramco Healthcare (JHAH), Saudi Arabia before and after the implementation of the antibiotic stewardship program. The study was approved by the Research Ethics Board of JHAH.

4.3 Duration of Study

The total study period was twelve years, six years before and six years after the implementation of the antibiotic stewardship program.

4.4 Stool samples and processing

Patient stool samples from were tested for toxigenic C. *difficile* (tCd) at Johns Hopkins Aramco Healthcare microbiology laboratory.Toxigenic C. *difficile* (tCd) was identified using Enzyme-linked immunosorbent assay (Premier Toxins A&B EIA; Meridian Bioscience) for C. *difficile* toxins A and B.

4.5 Case definitions

A case of CDI was defined as a patient with a stool positive test for C. *difficile* toxin A and/or B by EIA.

A case of CDI recurrence was defined as a patient with a stool positive test for C. *difficile* toxin A and/or B by EIA 2-8 weeks after the last positive test.

A case of C. *difficile* re-infection was defined as patient with a stool positive test for C. *difficile* toxin A and/or B by EIA more than 8 weeks after the first positive test. The defintions are based on CDI surveillance recommendations of the Centre for Disease Control (CDC/McDonald *et al* 2007).

4.6 Procedure/Data Collection

A retrospective review of the JHAH laboratory management system was conducted to identify all stool samples tested for toxigenic C. *difficile* (tCd) over the study period (2005-2016). The medical record number is routinely used by the microbiology as a unique identifier to link a patient to a tCd test result. Anonymised demographic data were received from the laboratory including only the patients' age, gender, and location of the patient at the time of sample collection. Surveillance screening is not standard practice at JHAH and the laboratory tests only unformed/diarrhoea stool for tCd. Therefore each test was considered clinically indicated, and a positive tCd test interpreted as a case of CDI.

For each patient testing positive for tCd, only the first positive test was counted, except where a subsequent tCd positive test met the case definition of a re-infection (see 4.4.) Patients were grouped into those who were tCd positive before and after the introduction of the antibiotic stewardship program (2005-10 and 2011-16 respectively). Patient information was exported to an excel sheet and kept on a personal PC. The PC was protected by secure log in and not connected to the internet.

4.7 Age groups of participants

The age group categories used were elderly (65 years and above), adult (18 to 64 years) and paediatric (3-17 years). Paediatric patients below the age of 3 were excluded from the study due to the propensity of the 0-2 age group for asymptomatic colonization with toxigenic and non-toxigenic C. *difficile* strains (American Academy of Paediatrics, 2013, Antonara and Leber 2016)

4.8 Metric

The period prevalence (%) of tCd was estimated by dividing the total number of test positive patients by the total number of patients tested over a specific period.

4.9 Data Analysis

Data was analysed using SPSS version 23 (SPSS Inc., Chicago, IL) for Windows. The Fisher exact test was used to test for differences in proportions. The Student t-test was used to compare the means of continuous variables. Two-sided P values less than 0.05 were considered statistically significant.

Chapter 5 Results

5.1 Pre and post-ASP tCd prevalence

Over the study period (2005 to 2016), a total of 3086 inpatients at Johns Hopkins Aramco hospital (JHAH) were tested for toxigenic C *difficile* (tCd). Two hundred and sixty (260) patients tested positive for tCd, giving an overall period prevalence of 8.4% (Table 8). There was a significant decline in tCd prevalence from 9.8% in the six year period preceding the launch of the ASP to 7.4% in the post-ASP implementation period (P=.022) There was no significant differences in tCd prevalence by gender, with females accounting for 139/260 (53%) and males 121/260 (47%) of tCd positive patients identified.

The 260 tCd positive patients included 12 patients who re-tested tCd positive more than 8 weeks after their initial positive test. These were considered new acquisitions of tCd (or re-infections) in line with the surveillance case definition (CDC/McDonald *et al* 2007) employed. and included in the period prevalence estimate, The majority of re-infections (8/12; 66%) were observed among the elderly. Re-infections were evenly distributed between the pre and post-intervention period (6 cases in each period).

28/260 (11%) tCd positive patients tested positive for tCD between 2 and 8 weeks of their initial positive test. In line with the study case definition, these were considered to reflect recurrences/relapses of CDI, and were not included in the prevalence estimates.

Most relapses (20/28; 71%) occurred in the post-intervention period with a significant (P=.018) increase in the recurrence rate from 6.2% (8/129) to 15.3% (20/131) in the pre-ASP and post-ASP periods respectively. The majority (18/28; 64%) of recurences were observed in the elderly.

The mean age of patients tested was 55 while the mean age of tCd positive patients was 59. Positive patients tended to be older than tCd negative patients (P<.05). Although the elderly comprised only 43% of patients tested, they accounted for more than half (143/260; 55%) of the total number of tCd positive patients (Fig. 1).

Table 8 Pre and post-ASP tCd prevalence

Study Period	# Patients Tested	# tCd positive	#Prevalence (%)	*P*-value
2005-10 (Pre ASP)	1318	129	9.8	.022
2011-16 (Post ASP)	1768	131	7.4	
2005-16	3086	260	8.4	

ASP-Antibiotic Stewardship Program

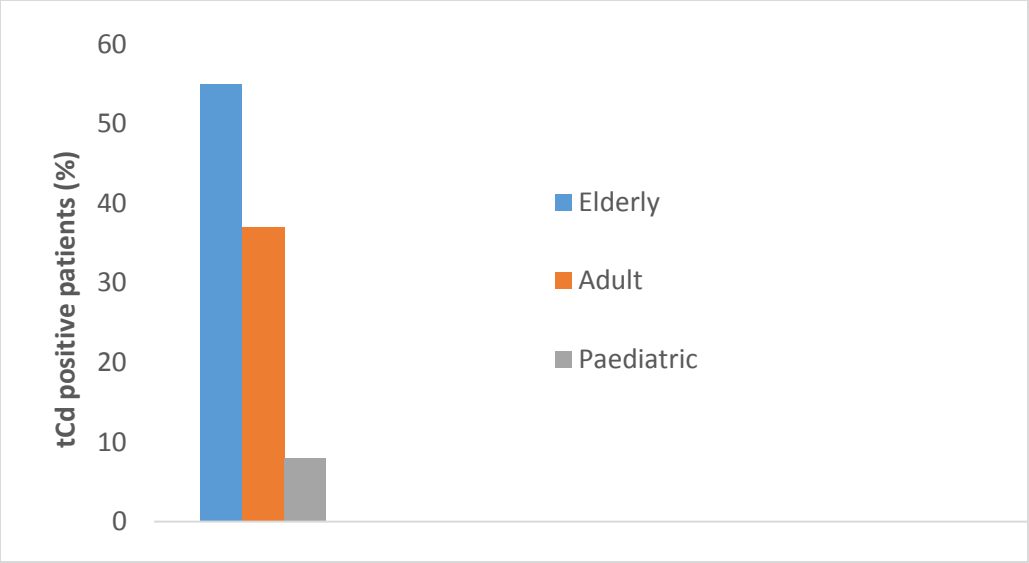

Figure 1. tCd positive patients by age group.

5.2 Pre and post-ASP tCd prevalence by age group

Age-group-specific tCd period prevalence was obtained by expressing the number of tCd positive patients in a specific age group as a proportion of the total patients in that age group tested. Age group specific tCd prevalence was observed to be significantly higher (P<0.05) among the elderly (65 years and above) compared to younger adult and paediatric patients (Table 9) A decline in tCd prevalence was observed in the period following the implementation of antibiotic stewardship. Although observed among all age groups, this decline was statistically significant (P=.002) only among paediatric patients (Table 9 Fig 2) The number of patients tested for tCd increased during the post-ASP period by 41%, 34% and 9% in elderly, adult and paediatric patients respectively.

Table 9 Age group-specific tCd prevalence pre and post ASP

Age group	number tested pre ASP	number positive pre ASP	Prevalence pre ASP	number tested post ASP	number positive post ASP	Prevalence post ASP	*P*-value
Elderly	548	64	11.7	775	79	10.2	.419
Adult	613	48	7.8	821	48	5.8	.084
Paediatric	157	17	10.8	172	4	2.3	.002
Total	1318	129	9.8	1768	131	7.4	.022

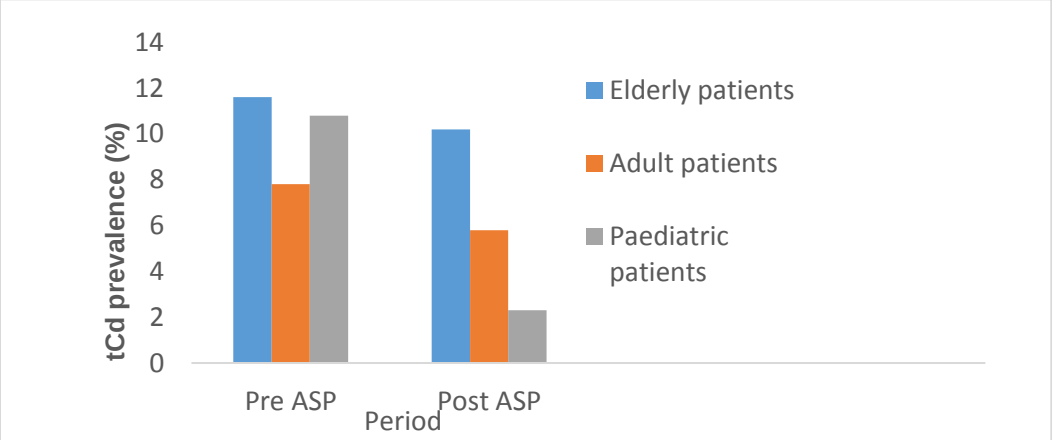

Figure 2. Age group specific tCd prevalence pre and post ASP.

5.3 Pre and post-ASP tCd prevalence by service unit

A break-down of tCd positive patients by service units revealed that tCd prevalence was highest in the cancer care and infectious disease units (Table 10) A significant decline in service-specific tCd prevalence was observed in paediatrics during the post-ASP period (P<.05) (Table 11). A non-significant decline in tCd prevalence was observed in all other services except cancer care, male surgical and cardiac telemetry where an increase in prevalence was observed. The increase in tCd prevalence in these three units was not statistically significant however.

Table 10 Service unit-specific tCd prevalence

Unit	Description	# tCd positive patients	#patients tested	Prevalence (%)
1A	Male medical	9	110	8.2
1B	Male surgical	9	152	5.9
2A	Infectious disease/Isolation	41	404	10.1
2B	Cardiac Telemetry	9	100	9
2C	Coronary Care	11	135	8.1
3A	Step down ICU	29	291	9.9
3B/5C	Medical ICU	23	315	7.3
3C	Surgical ICU	7	149	4.7
3H	Mother and Baby Unit	2	61	3.3
4H	Female Medical and Surgical	16	206	7.7
5A	Female Medical	40	504	7.9
5B	Cancer care	42	276	15.2
5G	Orthopaedics	11	153	7.2
6A/6B	Paediatrics	9	168	5.4
6C	Paediatric ICU	2	51	3.9
Total		260	3075**	8.4

**The total excludes 11 patients on 3 units without a positive tCd patient pre and post ASP

Table 11 Service unit-specific tCd prevalence pre and post ASP

Unit	Description	Pre ASP tCd prevalence (%)	Post-ASP tCd prevalence (%)
1A	Male medical	21	4.6
1B	Male surgical	5.1	6.2
2A	Infectious disease/Isolation	11.7	8.8
2B	Cardiac Telemetry	3.8	10.8
2C	Coronary Care	9.6	5.7
3A	Step down ICU	13.8	8.1
3B/5C	Medical ICU	7.6	6.9
3C	Surgical ICU	5.9	3.1
3H	Mother and Baby Unit	4	2.7
4H	Female Medical and Surgical	12.3	5.3
5A	Female Medical	9.3	7
5B	Cancer care	14	15.9
5G	Orthopaedics	8.5	4.2
6A/6B	Paediatrics	9.1	2.2
6C	Paediatric ICU	6.8	0

5.4 Secular trends in tCd prevalence

The antibiotic stewardship program began in late 2010 starting with restricted reporting of antibiotic susceptibilities of specific organisms. This was followed by prescriber and pharmacy in-service educational sessions in 2011. The majority of interventions were implemented in 2012, consisting of automatic renal dosing, antibiotic de-escalation protocol, intravenous to oral conversion program, vancomycin pharmacokinetic monitoring, pre-operative antibiotic protocols using adapted orders, and strategies to enhance judicious prescribing for upper respiratory tract infections in paediatric outpatient clinics. All patient and age-group specific tCd prevalence was observed to fluctuate in the six years (2005-10) preceding the implementation of the stewardship program. (Figures 3-6). This appeared to stabilize in the three years following the implementation of

stewardship, and a decline in tCd prevalence was observed in 2013. However, with the exception of paediatric patients, this decline was reversed after 2014.

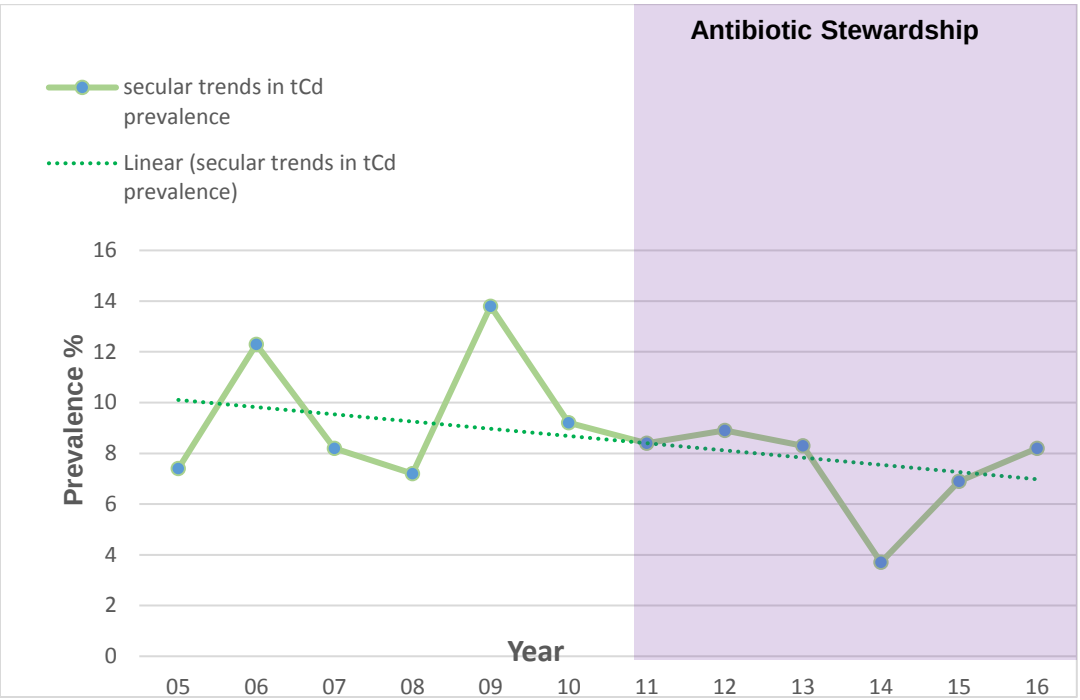

Figure 3. Secular trends in tCd prevalence (all in-patients).

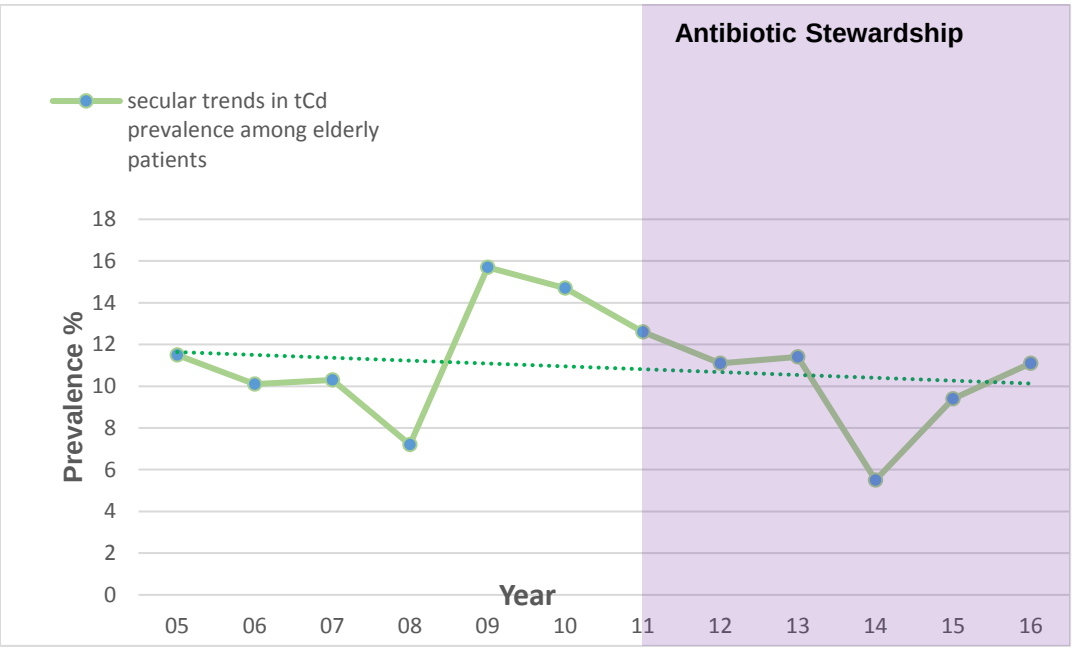

Figure 4. Secular trends in tCd prevalence among elderly patients.

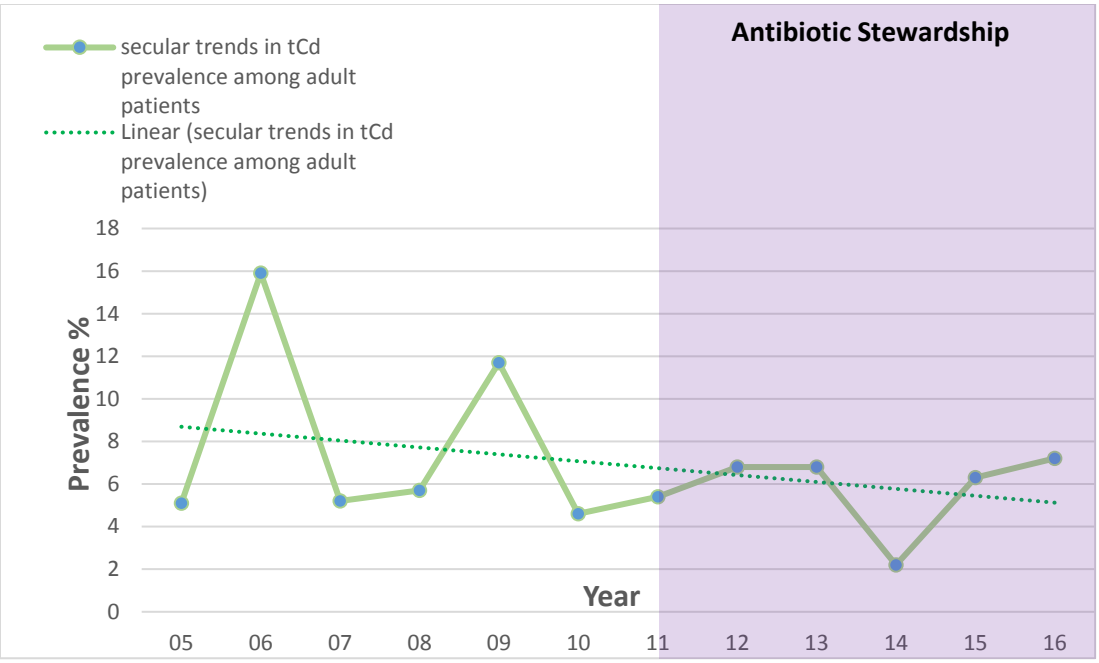

Figure 5. Secular trends in tCd prevalence among adult patients.

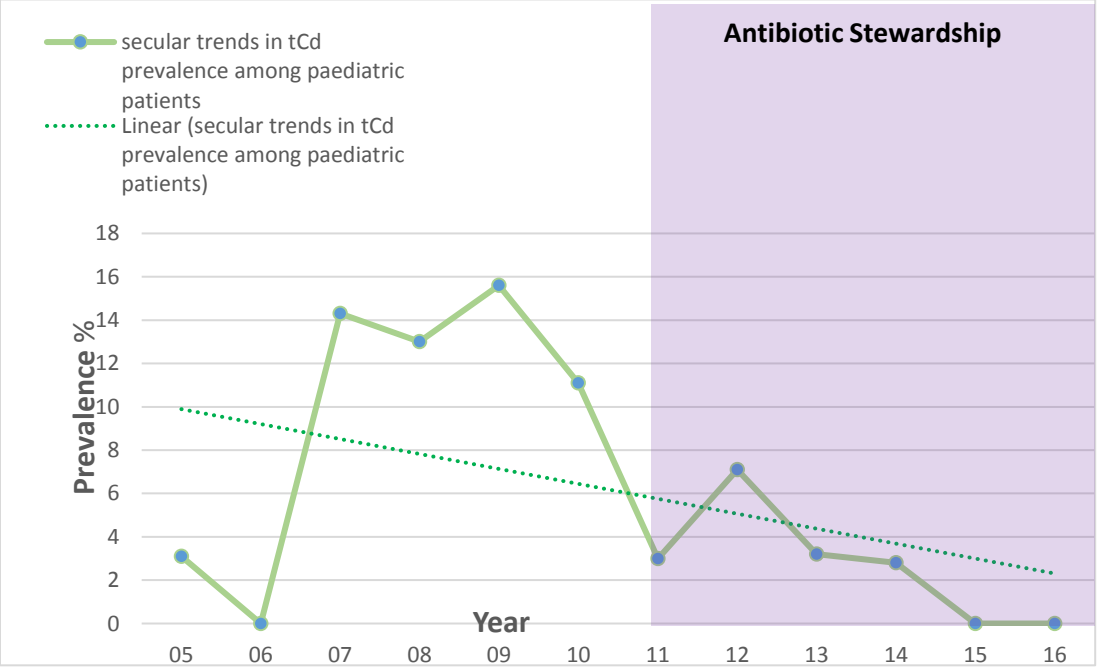

Figure 6. Secular trends in tCd prevalence among paediatric patients.

5.5 Impact of antibiotic stewardship on antibiotic consumption

Data on antibiotic consumption was not available for the whole study period. The only available data in WHO defined daily doses (DDD) was obtained from a report published by the antibiotic stewardship team at JHAH (Momattin *et al*, 2018) and covers only 4 years in the post-intervention period (2011, 2013, 2014 and 2015). Since DDD is based on adult doses, paediatric antibiotic consumption was excluded in this report. The total DDD was 38,270 in 2011, 37,557 in 2013, 36,550 in 2014, and 38,738 in 2015. In 2013, the hospital experienced an outbreak of the Middle East Respiratory Syndrome coronavirus (MERS-coV). Excluding antimicrobials given to patients suspected or confirmed with MERS-coV from 2013, the DDD declined from 38,720 in 2011 to 35,942 in 2015 (Table 12) Antibiotic consumption data for 2012 was omitted from the report since most interventions were implemented in that year.

Table 12 Secular trends in antibiotic consumption post ASP

Year	2011	2013	2014	2015
Antibiotic consumption in DDD	38,720	37,557	36,550	38,738/35,942*

* adjusted for antibiotic use during the post-MERS coV outbreak period

Chapter 6 Discussion

6.1 Comparative review of outcomes

This study began with an enquiry on whether a hospital antibiotic stewardship program could have a meaningful impact on the prevalence of CDI in Saudi Arabia, a setting of unregulated public access to antibiotics and where self-medication with antibiotics is the norm. The hypothesis was that toxigenic C. *difficile* (tCd) is highly prevalent (but under-estimated) in Saudi communities due to the selection pressure imposed by long term unregulated antibiotic exposure among members of the public. That being the case, any gains made by a hospital antibiotic stewardship program in reducing the rate of C *difficile* infection (CDI) would be offset by the high burden of patients admitted to the hospital with tCd, resulting in a null effect.

The results of this study do not lend support to this hypothesis, and a statistically significant decline in tCd prevalence was observed in the six year period following the implementation of antibiotic stewardship. This was an unexpected finding, considering especially that the ASP was limited primarily to supplemental interventions (prescriber and pharmacy education, renal dose monitoring, pharmacy-led vancomycin monitoring, intravenous to oral antibiotic streamlining, de-escalation from broad to more narrow spectrum antibiotics and a multifaceted intervention to reduce inappropriate treatment of upper respiratory tract infections in paediatric outpatient clinics).

It is plausible that the limited nature of the interventions was compensated for by the services and leadership role of the infectious disease consultant prior to and during the formal implementation of the ASP. This would be consistent with other ASP studies (Jump

et al 2012, Tedeschi *et al* 2017l; Appendix 1) that have reported significant reductions in the rate of CDI with ID consultation either alone or in combination with one or more supplemental interventions. Ostrowsky *et al* (2018) highlight the advantages of an ID physician led-ASP, among which is a greater level of buy-in to the program by physician (prescribers) peers. It is therefore not unlikely that the leadership of the ID physician had the impact of enhancing prescriber collaboration with ASP recommendations. This would have been especially applicable to the strategies of broad spectrum de-escalation and switching from intravenous to oral antibiotic dosing, two interventions that are often challenging to implement and require clinical consensus (Septimus and Owen, 2011)

Despite the significant decline in tCd prevalence post-ASP, when broken down by age group, this outcome was significant only among paediatric patients. The outcome in paediatric patients is perhaps related to the relatively lower burden of CDI in this age group. It is also possible that the multi-faceted stewardship interventions specifically implemented in paediatric outpatient clinics may have influenced prescribing practices (and by proxy tCd prevalence) on the in-patient wards, since both settings are served by the same paediatricians.

It was not possible to compare the outcome among paediatric patients with the ASP literature since none of the studies reviewed specifically described the impact of stewardship interventions in this patient population. Similarly, in a systematic review of antibiotic stewardship in paediatric settings Smith *et al* (2015) were also unable to identify a study reporting the impact of antibiotic stewardship on the rate of CDI in paediatric

patients, despite a growing recognition of this disease as a cause of nosocomial diarrhea in children (Feghaly-Tarr 2013, Sammons *et al* 2013)

The reasons for the non-significant decline in tCd prevalence among elderly patients are also unclear. However this outcome may be related to the broad scope of the stewardship program, as this high risk group was not specifically targeted for intervention. Feazel *et al* (2014) observed that studies reporting the strongest association between stewardship interventions and a reduced rate of CDI in the elderly were based on programs specifically targeting this age group. This is consistent with the review conducted in the current study. 9/9 (100%) programs exclusively targeting the elderly (McNulty *et al* 1997, Stone *et al* 1998, Ludlam *et al* 1999, O'Connnor *et al* 2004, Fowler *et al* 2007, Starks *et al* 2008, Gulihar *et al* 2009, Jump *et al* 2012 and Beaulac *et al* 2016) reported a significant decline in the rate of CDI (appendix 1)

The lack of a significant outcome among the elderly may also be related to the relatively higher burden of CDI observed in this group. The predominance of the elderly among patients meeting the case definitions for CDI re-infection and recurrence is also indicative of higher level of CDI severity, probably facilitated by clinical co-comorbidities.

While recurrent cases were not counted in the prevalence estimate, the observed rate of 11% is a useful estimate of the increased risk among patients with a history of CDI and also highlights the importance of this often neglected aspect of stewardship. The observation of the highest tCd prevalence in the cancer care unit is consistent with the

role of immunodeficiency as a risk factor for CDI and highlights the need for the antibiotic stewardship program to also target this high risk group.

The predominantly supplemental nature of the interventions of the ASP may also explain the non-significant reduction in tCd prevalence observed among adult and elderly patients. A more significant impact may have been observed if the program included one or more of the core stewardship interventions, especially formulary restriction and preauthorization of broad spectrum high CDI risk antibiotics. In a systematic review Feazel *et al* (2014) observed that antibiotic stewardship is most effective in reducing the rate of CDI when formulary restriction is a component of the program. This observation was also made in the literature review conducted in the current study (section 2.1, table 2). The absence of formulary restriction and pre-authorization of antibiotics meant that prescribers to a large extent, maintained autonomy and were not obliged to comply with stewardship recommendations.

Another possible reason for the inability to observe a significant association between the antibiotic stewardship program and a reduction in the rate of tCd among adult and elderly patients is inappropriate testing of formed stool or testing stool without ruling out other causes of diarrhoea. The significant increase in the number of tCd tests in the post-antibiotic stewardship period suggests that this may have occurred. This may have identified asymptomatically colonized patients and masked pre and post ASP differences in tCd prevalence.

The study outcome may also have been influenced by the outbreak of the Middle East Respiratory Syndrome coronavirus (MERS coV) that occurred at JHAH in 2013. MERS coV is a febrile respiratory illness that was identified in Saudi Arabia in September 2012 (Al-Tawfiq *et al* 2014) This outbreak has been associated with a high level of mortality and morbidity throughout the country. Although of a viral aetiology, MERS-coV is often associated with opportunistic bacterial infections.

Over a two month period (April to May 2013), a total of 99 patients at JHAH met the case-definition for MERS coV. Of this total, 17 tested positive. Although paediatric cases were observed, the majority of suspected and confirmed cases of MERS were middle aged adults or elderly. The mean age of cases was 60.7 with a range of 5 to 92 years (Al-Tawfiq *et al* 2014). Suspected cases of MERS coV continued to be identified in the study hospital over the rest of the study period (2013 to 2016) although no additional confirmed cases were identified.

There is no specific treatment for MERS coV but due to the risk of opportunistic bacterial infections, antibiotic use is often a component of the supportive management of this disease. It is plausible that even after the outbreak peak, ongoing surveillance and identification of patients suspected with MERS coV may have had the residual impact of increasing prophylactic and empiric antibiotic use in the hospital over the rest of the study period. Although speculative this assertion is consistent with the report of the antibiotic stewardship pharmacy team (Momattin *et al* 2018) of a 2,188 DDD increase in antibiotic consumption between 2014 and 2015 attributable to MERS coV.

Therefore increased antibiotic exposure in adult and elderly patients suspected with MERS coV may partially explain the reversal in the downward trend in tCd prevalence observed from 2014, and the overall lack of impact of the stewardship program on adult and elderly patient. Another consideration is that since diarrhea is a common presentation in patients with MERS coV, it is plausible that the observed increase in the number of requisitions for tCd testing in the post-antibiotic stewardship period is related to a general increase in testing for infectious gastroenteritis in patients suspected with MERS coV.

In their review of tCd in Asia, South America and Africa, Roldan *et al* (2018) observed a prevalence range of 8.3-27.9%. The tCd prevalence rates of 9.8% and 8.4% observed in the pre and post ASP periods respectively are consistent with those reported in Europe (Bauer *et al* 2011; 4-39%), and North America (Cohen *et al* 2014 6.9-20.4%) where CDI is more recognized as a public health threat. These findings are consistent with the hypothesis of a high tCd prevalence in Saudi Arabia, considering especially the low sensitivity of the EIA test method employed in the study.

It was hypothesized that due to the extent of antibiotic consumption including the common-practice of self-medication with antibiotics in Saudi Arabia, tCd prevalence among patients admitted to the hospital would be too high for stewardship interventions to have any detectable impact. This hypothesis is supported by studies linking asymptomatic tCd colonization with an increased risk of symptomatic disease during hospitalization (Zacharioudakis et al. 2015, Caroff et al 2017, Lin et al 2015, Nissle et al 2016, Blixt et al 2017, Deshpande et al 2015, Kagan et al 2017, Baron et al 2019).

One possible reason why asymptomatic tCd carriage may have had less than the anticipated impact on the rate of CDI is the relatively young age of the study population. The mean age of the patients that presented with diarrhoea and tested positive for tCd was 55. Although CDI appears to be on the increase in younger adults and children, it is still predominantly associated with the elderly (65 years and above). It may be that more patients were colonized with tCd than were detected, since detection was reliant on the testing of only symptomatic patients (presenting with unformed/diarrhea stools) Due to immuno-suppression and a greater level of co-morbidities, symptomatic patients are more likely to be elderly as evidenced by the higher tCd prevalence in this age group. There are indications that the Saudi population is aging however. Life expectancy has increased from age 63 in 1980 to 73 in 2010 United Nations, World Population Prospects 2012) (appendix 4) .This trend is likely to continue, the implication being that the prevalence of tCd will increase as the Saudi population ages, particularly if current antibiotic consumption trends are maintained.

These observations are consistent with the rationale of the current study and lend support to a proposal for pre-admission screening of high risk patients (elderly, multiple co-morbidities, immunocompromised) for tCd.

6.2 Study limitations

The retrospective, before-after intervention design of this study limits the extent to which the observed decline in tCd prevalence can be attributed to the antibiotic stewardship

program. The observed outcome may be related to other interventions that occurred in the pre and post intervention period or regression to the mean. The incorporation of interrupted time series analysis into the design would have facilitated the interpretation of the secular trends observed. Other factors that may have influenced the study outcome include the activities of the infectious disease consultant (as previously described) In addition, infection control practices and the hand hygiene program preceded antibiotic stewardship and were ongoing over the course of the study.

It is interesting that some studies have not considered concurrent infection control activities as a limitation in their evaluation of the impact of antibiotic stewardship. All five studies in the current review that described bundles consisting of antibiotic stewardship, infection control and hand hygiene (Stone *et al 1998,* Muto *et al* 2007, Valiquette *et al*; 2007, Price *et al* 2010, Cook and Gooch 2015) observed significant reductions in the rate of CDI. In their systematic reviews, Feazel *et al* (2014) and Baur *et al* 2017 also associated bundled interventions with reductions in the rate of CDI. It appears that bundling is an effective strategy to enhance antibiotic stewardship impact, even though it may have been coincidental in the current study.

The validity of tCd prevalence as a metric of antibiotic stewardship impact on CDI is limited when testing for tCd occurs without sufficient consideration given to ruling out other possible causes of diarrhea. The increase in the number of tCd tests observed suggests this may have occurred over the study period. If so, an unknown number of tCd positive patients may represent asymptomatic colonization with diarrhoea attributable to

iatrogenic factors, rather than CDI. Inability to control for inappropriate tCd testing is therefore a study limitation. However, inappropriate testing for tCd is a source of bias common to all studies estimating the impact of antibiotic stewardship on the rate of CDI, regardless of the metric used.

Another limitation of the study was the lack of data on antibiotic consumption volume and prescribing patterns over the study period. This would have provided additional insights regarding the impact of the stewardship program on the type, dose and duration of use of different antibiotic groups, especially high CDI risk agents. Nevertheless, it is noteworthy that the downward trend in overall antibiotic consumption observed post stewardship is consistent with the trend in tCd prevalence over the same period.

The relatively low sensitivity of Enzyme-linked immunosorbent assay (EIA) used to identify tCd may have underestimated the observed tCd prevalence, and influenced the study outcome. A molecular test or cytotoxic culture is likely to have enhanced the yield of positive tests. In a multi-hospital study Cohen *et al* (2014) observed that laboratories introducing nucleic acid amplification testing (NAAT) as first-line tests for C .*difficile* had a mean increase of 45% in C. *difficile* positivity rates. If employed in the current study, this may have had the net effect of nullifying the observed outcome. On the other hand a greater yield of tCd positive patients may have increased the power to observe a difference in pre and post stewardship tCd prevalence.

It is also plausible that there were enhancements over the twelve year study period in the sensitivity of the EIA test kit used. This could also have biased pre and post intervention comparison. There is no evidence that this occurred however.

The study was also unable to examine prescriber perceptions and attitudes towards the stewardship program, and their level of compliance with recommendations.
This is a limitation since it may have shed light on the study outcome, such as the significant decline in CDI prevalence observed in paediatric patients, the non-significant impact of the program on adult and elderly patients, and changes in prescribing practices that reversed the downward trend in tCd prevalence observed prior to 2014.

Despite this limitation, a previous report (Al Tawfiq *et al* 2015) from the same hospital provides some indication of prescriber attitudes to the stewardship program over the study period. Al Tawfiq *et al* (2015) report that following the introduction of restricted antibiotic susceptibility reporting, the infectious disease physician and pharmacist received enquiries from prescribers wishing to use specific antibiotics but unable to access microbial susceptibility reports for these agents. Such prescriber preferences suggest that the predominantly persuasive elements of the stewardship program may have had limited impact on prescribing practice.

A final limitation is with respect to the study setting. In a number of ways, Johns Hopkins Aramco Healthcare (JHAH) is unique among other hospitals in Saudi Arabia. It is a private organization and a large proportion of the population served are staff and family members

of the parent Saudi Aramco Company. In terms of its services and the health seeking behavior of its patients, including self-medication with antibiotics, JHAH may not be typical of many hospitals in Saudi Arabia. It is therefore plausible that the study outcome may only be replicable in similar settings in the country.

6.3 Conclusion

The results of the study indicate that despite the likelihood of a high burden of C. *difficile* infection (CDI) in the community, a hospital antibiotic stewardship program in Saudi Arabia can reduce the prevalence of CDI among hospitalized patients. Furthermore the findings indicate that this impact can be quantified by measuring the period prevalence of toxigenic C. *difficile* in unformed/diarrhoea patient stool, despite the inability of this metric to distinguish community-acquired and nosocomial C. *difficile* infection. Employing this metric will however require on-going engagement of physicians and microbiology laboratory personnel to ensure that repeat testing of specimens for cure is avoided, and consistency is maintained in the practice of testing only unformed or diarrhoea stool. This will enhance the CDI predictive value of a positive tCd test. The elements of the JHAH antibiotic stewardship program will also need to be enhanced. Evidence from antibiotic stewardship studies including systematic reviews supports a recommendation for the inclusion of formulary restriction and pre-authorization of high risk for CDI agents as a stewardship element, and bundling antibiotic utilization and infection control interventions into a single program. These interventions have been most strongly associated with reduction in the rate of CDI. A bundled hospital antibiotic stewardship program would not only reduce the risk of incident and recurrent CDI by promoting the judicious use of

antibiotics, but at the same time ensure consistent and timely application of infection control best practices to reduce tCd transmission in the hospital.

The significantly higher prevalence of tCd observed in elderly patients is consistent with other studies and is indicative of the relatively higher risk of both tCd colonization and CDI in this age group. In light of the additional risk of CDI to the tCd carrier, and the risk of tCd transmission from carrier to other patients and health care workers, the impact of the antibiotic stewardship program would be enhanced by the implementation of admission screening of the elderly for tCd. Given the increased risk of CDI recurrence following repeated antibiotic exposure, knowing the tCd carrier status of admitted elderly patients would guide appropriate prescribing in this vulnerable group. It would also ensure the timely implementation of appropriate infection control measures to limit hospital transmission of tCd.

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APPENDIX 1 Studies of antibiotic stewardship and impact on CDI

Study/Country/Setting	Interventions	Metric	Outcome
Aldeyab *et al* 2012/UK/Hospital	Antibiotic prescribing guidelines, education, restriction of CDI high risk antibiotics,	CDI incidence/100 occupied bed days /month	Significant decline in CDI incidence
Al-Tawfiq *et al* 2015/Saudi Arabia/Hospital	Restricted reporting of antibiotic susceptibility	CDI incidence/1000 patient days	Significant decline in CDI incidence
Amer *et al* 2013/Saudi Arabia/Hospital/ICU	Prospective audit of the use of 5 target broad spectrum antibiotics with feedback to prescribers	Not Stated	No significant impact
Beaulac *et al* 2016/Long Term Acute Care Hospital/USA	Telemedicine stewardship-remote access to medical records and usage of targeted broad spectrum antibiotics with email feedback/recommendations to prescribers	Monthly hospital-acquired CDI incidence /1000 patient days	Significant decline in CDI incidence
Bond *et al* 2017/Australia/multisite (5 hospitals)	Restriction of targeted antibiotics, Computer-based clinical decision support, prescriber education, guidelines,	Healthcare-associated CDI incidence /10,00 bed days/month	Significant decline in montlhly CDI incidence
Borde *et al* 2015/Germany/Hospital	Revised antibiotic guidelines discouraging cephalosporins and Fluoroquinolones, daily rounds by infectious disease physician	Nosocomial CDI incidence/ 1000 patient days	No significant impact
Bouza *et al* 2007 Spain/Hospital/ventilated patients with LRTI	Rapid E testing of respiratory samples (patients with suspected ventilator-associated infections)	CDI incidence proportion (%)	Significant difference between Interventions and control groups in CDI incidence proportion
Campbell *et al* 2017/ Canada/Hospital	Education, prospective audit	Hospital-acquired CDI incidence/1000 patient days	No significant impact
Carling *et al* 2003/ USA/Hospital	Prospective audit of antibiotic use with feedback	Nosocomial CDI incidence/1000 patient days	Significant decline in CDI incidence

APPENDIX 1 (continued) Studies of antibiotic stewardship and impact on CDI

Study/Country/Setting	Interventions	Metric	Outcome
Chan *et al* 2011/ Taiwan/Hospital	Prospective audit of prescriptions with prescriber feedback, Education	Incidence of Culture confirmed C. difficile	No significant impact
Climo *et al* 1998/ USA/Hospital/Outbreak	clindamycin restriction	Nosocomial CDI incidence /1000 discharges per month	Significant decline in monthly CDI incidence
Cook and Gooch (2015)/ USA/Hospital	Antibiotic guidelines, audit and feedback to prescribers and infection control Interventions	CDI incidence/10,000 patient days	Significant decline in CDI incidence then increase due to more sensitive test method
Cook *et al* 2011/ USA/Hospital	Electronic Medical Record, enhanced chart reviews and antibiotic use recommendations	CDI incidence/10000 patient days	No significant impact
Cruz-Rodriguez *et al* 2014/Mexico/Hospital/ Orthopaedic ward	clindamycin restriction	Nosocomial CDI incidence /1000 hospital days	No significant impact
Dancer *et al* 2013/ UK/Hospital	Restriction of ceftriaxone and ciprofloxacin, education	Hospital-acquired CDI incidence /1000 patient beds	Significant decline in CDI incidence
DiDiodato and McArthur 2016/ Canada/Hospital/General Medical and Surgical wards	Prospective audit with prescriber feedback	Healthcare -associated CDI/1000 patient days	Significant decline in CDI incidence on medical ward but NOT surgical wards
Dubrovskaya *et al* 2012/USA/Surgery	Antibiotic guidelines targeting reduction in use of specific antibiotics for intra-abdominal infections	CDI incidence /1000 patient days	No significant impact
Elligsen *et al* 2012/ Canada/Hospital/ICU	Prospective audit with prescriber feedback	Monthly incidence of nosocomial CDI	Significant decline in number of nosocomial CDI cases
Fowler *et al* 2007/ UK/Hospital/Geriatric	Prospective audit with prescriber feedback	CDI incidence rate ratio	Significant decline in CDI incidence rate ratio
Giacobbe *et al* 2017/ Italy/Hospital	Education, semi-restrictive antibiotic policy, pre-authorization and feedback	Healthcare-associated CDI incidence/1000 patient days	No significant impact
Gulihar *et al* 2009/ UK/Hospital/Orthopedic units/Geriatric	Formulary restriction of cephalosporins, change in antibiotic policy for diarrhea, surgical prophylaxis cephalosporin to co-amoxiclav	CDI incidence (%)	Significant decline in CDI incidence

APPENDIX 1 (continued) Studies of antibiotic stewardship and impact on CDI

Study/Country/Setting	Interventions	Metric	Outcome
Jenkins *et al* 2015/USA/Hospital	Pre-authorization of selected antibiotics, prospective audit and feedback, local Guidelines, intravenous to oral, physician and pharmacy Education, physician champions	Hospital-onset CDI incidence/1000 patient days	No significant impact
Jump *et al* 2012/USA/Long term care facility	Infectious disease consultation	Number of positive C. difficile tests/1000 days of care	Significant decline in CDI from increasing to a decreasing trend post-Intervention
Kallen *et al* 2009/USA/Hospital/outbreak	Fluoroquinolone restriction	Hospital-onset CDI incidence/1000 patient days	Significant decline in hospital onset CDI incidence
Kandel *et al* 2016/Canada/Hospital/2 internal medicine wards	Computerized order entry alert for PPI and antibiotics, prospective audit and feedback	Hospital-acquired CDI Incidence/100 patient days	No significant impact
Khan and Cheesbrough 2003/ UK/Hospital	Antibiotic switch-Cephalosporin to levofloxacin for community acquired sepsis/ pneumonia	CDI incidence/1000 occupied beds	Reduction in nosocomial CDI No test of significance reported
Leung *et al* 2011/Canada/Hospital (intensive care)	Prospective audit of antibiotic use (particularly broad spectrum anti-pseudomonal agents) with prescriber feedback	Hospital acquired CDI incidence/1000 patient days	No significant impact
Libertin *et al* 2017/USA/Rural community Hospital	Prospective audit and feedback, prescriber education (grand rounds, local antibiogram	Nosocomial CDI incidence/1000 occupied beds	Significant decline in Nosocomial CDI incidence
Ludlam *et al* 1999/ UK/Hospital/geriatric wards	Restriction of third generation cephalosporins	Incidence of CDI	Significant decline in CDI incidence
Malani *et al* 2013/ USA/Community Hospital	Prospective audit of target antibiotics with feedback	Cumulative CDI Incidence	Significant decline in cumulative CDI incidence proportion
McNulty *et al* 1997/UK/Hospital (Geriatric) CDI outbreak	Restrictive antibiotic policy to limit use of cephalosoprins (cefuroxime)	Incidence of CDI	Significant decline in CDI incidence
Moffa *et al* 2018/USA/Hospital	Preauthorization, Formulary restriction, Prospective audit and feedback, Education sessions	Healthcare-associated CDI incidence/1000 patient days	Significant decline in incidence of healthcare-associated CDI
Morrill *et al* 2016/USA/Hospital	Prospective audit of antibiotic prescribing and feedback	Mean CDI incidence /10,000 patient days	No significant impact

APPENDIX 1 (continued) Studies of antibiotic stewardship and impact on CDI

Study/Country/Setting	Interventions	Metric	Outcome
Muto *et al* 2007/USA/Hospital (CDI outbreak)	Restriction of clindamycin, ceftriaxone, levofloxacin, other broad spectrum antibiotics, infection control	Hospital acquired CDI incidence/1000 hospital discharges	Significant decline in CDI incidence
Nowak *et al* 2012/ USA/Hospital	Prospective audit and feedback	Quarterly CDI incidence/1000 patient days	Significant decline in CDI incidence
Nuila *et al* 2008/ USA/Hospital	Pre-authorization of intravenous antibiotics	CDI incidence/1000 bed days	Significant decline in CDI incidence
O'Connor *et al* 2004/ Ireland/Hospital/Geriatric	Change in antibiotic policy, restriction of IV cephalosporin antibiotics	CDI incidence per 100 antibiotic defined daily doses (DDD)	Significant decline in CDI incidence
Ostrowsky *et al* 2014/ USA/Hospital (multi-centre)	Prospective audit of high risk for CDI antibiotics with feedback to prescribers	Hospital onset CDI incidence/ 10,000 patient days	No significant impact
Palmay *et al* 2014/ Canada/Hospital	Education, audit and feedback on appropriate use of target antibiotics (carbapenems, cephalosporins, fluoroquinolone and vancomycin)	Nosocomial CDI incidence/1000 patient days	No significant impact
Patton *et al* 2017/UK/Hospital (medical and surgical wards)	Restricted use of high risk antibiotics, cefuroxime, ceftriaxone, clindamycin, clarithromycin, fluoroquinolone and co-amoxiclav	CDI incidence/1000 admissions	No significant impact
Price *et al* 2010/ UK/Hospital	Cephalosporin and fluoroquinolone restriction, infection control	Nosocomial CDI incidence/1000 patient days	Significant change in rate of decline in nosocomial CDI incidence
Sarma *et al* 2015/ UK/Hospital	Fluoroquinolone restriction, audit and feedback, guidelines	hospital-acquired CDI incidence/100,000 occupied bed days	Significant and sustained decline in hospital-acquired CDI incidence
Schon *et al* 2011/ Sweden/Hospital	Guidelines to reduce Cephalosporin, Fluoroquinolone use; compliance monitoring	Incidence of CDI	No significant impact
Shea *et al* 2017/ USA/Hospital (multi-centre)	Fluoroquinolone restriction. Education on appropriate fluoroquinolone use	Hospital-acquired CDI incidence/10,000 patient days	Significant decline in mean monthly CDI incidence

APPENDIX 1 (continued) Studies of antibiotic stewardship and impact on CDI

Study/Country/Setting	Interventions	Metric	Outcome
Starks *et al* 2008/ UK/Hospital/Orthopaedic Surgery/Geriatric	Revised antibiotic protocol; reduction in cephalosporin dosage for hip surgery prophylaxis	CDI incidence/100 patients at risk	Significant decline in CDI incidence in hip surgery
Stone *et al* 1998/ UK/Hospital/Geriatric	Formulary restriction of Cephalosporin antibiotics, Hand hygiene, feedback of CDI rates to frontline staff	CDI incidence/100 admissions	Significant reduction in CDI incidence
Storey *et al* 2012/USA/Hospital	Prospective audit of prescriptions with feedback to prescribers	Healthcare facility-onset CDI incidence/10000 patient days	No significant impact
Taggart *et al* 2015/ Canada/Hospital/ICU	Prospective audit of antibiotic use and feedback	Nosocomial CDI incidence/1000 patient days	No significant impact
Talpaert *et al* 2011 UK/Hospital	Revised empiric treatment guidelines restricting use of broad spectrum antibiotics	Monthly CDI incidence/1000 occupied bed days	Significant decline in CDI incidence
Tedeschi *et al* 2017/Italy/Rehab Hospital	Prospective audit and feedback, Revised antibiotic protocol, education	CDI incidence/10,000 patient days	Significant decline in CDI incidence
Thomas *et al* 2002/ Australia/Hospital	Formulary restriction, pre-approval of ceftriaxone, Antibiotic policy to reduce third generation cephalosporin use	CDI incidence/1000 hospital discharges	Significant decline in CDI incidence
Valiquette *et al* 2007/Canada/CDI outbreak	Guidelines and education to, audit of compliance and feedback	Nosocomial CDI incidence/1000 patient days	Significant decline in CDI incidence to pre-outbreak levels
Wenisch *et al* 2014/ Austria/Hospital	CDI-related education Formulary restriction of Moxifloxacin.	Incidence of nosocomial CDI	Significant decline in Nosocomial CDI incidence
Yam *et al* 2012/ USA/Hospital	Prospective audit of prescribing with prescriber feedback, streamlining of therapy, dose optimization, education, infection control	Hospital-acquired CDI incidence/10,000 patient days	Unknown significance-decline in Hospital -acquired CDI incidence
Yu *et al* 2014/ USA/Hospital (two sites)	Post-prescription review of anti-pseudomonas and anti-MRSA agents, fluoroquinolones with prescriber feedback	Hospital onset, healthcare-associated CDI incidence/10,000 patient days	No significant impact

APPENDIX 2 Antibiotic stewardship studies in Saudi Arabia

Study	Design/Setting	Intervention	Duration	Outcome
Dib *et al* 2009	Before and After/Hospital	Implementation of intravenous vancomycin use guidelines, Prescriber education, chart reviews to monitor compliance and feedback	6 months: 3months pre-intervention, 3 months post intervention	Increase in compliance with elements of the guideline: empiric and specific treatment, prophylactic use and trough monitoring
AlAwdah *et al* 2015	Retrospective cohort/Hospital (Pediatric ICU)	Infectious disease physician rounds, audit and feedback to prescribers, Education	8 months from date of implementation	Decrease in days of therapy (DOT) for vancomycin, piperacillin-tazobactam, Meropenem
Alshukairi *et al* 2016	Before and After/Hospital	Change in Antibiotic policy for patients with febrile neutropenia;	2 years (1 year pre and 1 year post intervention)	Non-significant increase in gram negative susceptibility to piperacillin-tazobactam.
Al-Somai *et al*	Before and After/Hospital	Audit of use of capsofungin (antifungal), imipenem and meropenem with feedback to prescribers	12 months (5 months pre-intervention, 7 months intervention)	Reduction in the duration of use of imipenem and meropenem, no impact on duration of capsofungin use
Al-Tawfiq 2013	Retrospective/Hospital	Infectious disease consult and review of physician prescription with feedback	4 years: 2006-2009	Change and discontinuation of initially prescribed antibiotic in 58.7% and 14.7% consultations respectively
Amer *et al* 2013	Before and After historically controlled/Hospital (Intensive care unit)	Prospective audit of empiric antibiotic use of targeted,) and feedback to prescribers	1 month	Significant increase in the appropriateness of empirical; prescribing No impact on CDI rate

APPENDIX 2 (continued) Antibiotic stewardship studies in Saudi Arabia

Study	Design/Setting	Intervention	Duration	Outcome
Al-Tawfiq *et al* 2015	Before and After/Hospital	Modification of Enterobacteriaceae and Pseudomonas aeruginosa susceptibility reporting panels; restricted reporting of target antibiotics (amikacin, ampicillin, cefazolin, cefepime, cefuroxime, piperacillin-tazobactam, aztreonam, ceftazidime, tobramycin, chloramphenicol, tetracycline, mezlocillin. piperacillin)	2 years: 16 months pre-intervention, 8 months post intervention	Varying increase and decrease in enterobacteriaceae and P. aeruginosa susceptibility to specific antibiotic Increased use of amoxicillin and ampicillin, piperacillin-tazobactam, ticarcillin-clavulanic acid, ceftriaxone,ceftazine, and levofloxacin Decreased use of Cefepime, Amikacin, Cefuroxime, Cefazolin Decrease in CDI rate
Momattin *et al* 2015	Before and After, historically controlled/Hospital	Pharmacy led intravenous Vancomycin dosing and monitoring	2 years: 1 year pre-intervention, 1 year post intervention	Increase in proportion of patients achieving and maintaining vancomycin therapeutic range, decrease in the duration of therapy and incidence of acute renal injury

APPENDIX 2 (continued) Antibiotic stewardship studies in Saudi Arabia

Study	Design/Setting	Intervention	Duration	Outcome
Alawi and Dawersh 2016	Before and After/Hospital	Prospective audit and feedback, Pre-authorization of restricted antibiotics	3.75 years: 1 year pre-intervention 2.75 years stepwise implementation from surgery to other units	Decrease in utilization of restricted antibiotics and costs, decrease in rate of Acinetobacter baumanii infections
Al-Tawfiq and Alawami 2017	Before and Afer/Hospital (Pediatric outpatient)	Prospective audit of prescriptions, feedback, small group discussions and education, academic detailing and peer comparison, rapid streptococcal antigen test (RSAT)	12 months	Decline in monthly inappropriate antibiotic use (12.3% at the start and 3.8% at the end) 50% reduction in antibiotic use attributed to use of RSAT
Jacobs *et al* 2003	Before and After/Hospital (Intensive care)	Antibiotic protocol for patients undergoing percutaneous dilatational tracheostomy (PDT)	63 months (33 months pre and 30 months post intervention)	Improvements in appropriate empiric prescribing for PDT patients and reduction in peri-operative infectious complications
Kilan *et al* 2017	Before and After/Hospital (gastrointestinal Surgery)	Modification of surgical antibiotic prophylaxis adapted order and inclusion in surgical policy, prospective audit of antibiotic prophylaxis, nurse to surgeon reminders for intra-operative re-dosing, education, monthly compliance reports	12 months	Improvements in use of adapted order, appropriateness of antibiotic prophylaxis (antibiotic selection, dosing and timing, and discontinuation) Reduction (non-statistically significant) in surgical site infections

APPENDIX 3 Studies of self-medication with antibiotics (SMA) in Saudi Arabia

Study	Number of respondents/ response rate	Prevalence of SMA (%)/	Source of antibiotics or information	Class of antibiotics reported	Indications for antibiotic use
Abobotain al 2013	(NR) 631 participants	11.6%	NR	NR	NR
Abujheisha *et al* 2017	NR/670 participants	NR	Pharmacist, physician, Friends	NR	Fever, respiratory symptoms
Aldhafar and Talat 2017	NR/420	28.8%	Pharmacy, friends, previous prescription	NR	Respiratory (sore throat, influenza)
Alghadeer *et al* 2018	NR/1264	34%	Pharmacy, friends and family, left over prescription, Previous experience with the antibiotics	amoxicillin-clavulanic acid, amoxicillin	Tonsillitis and pharyngitis (76.7%)
Aljadhey *et al* 2015	538/707 (76%)	NR/	Pharmacy friends, family	NR	NR
Al-Qahtani *et al* 2018	NR/519	NR	Pharmacy (55.6%), previous experience, available antibiotics at home	NR	Respiratory (73%), digestive illness (12%) High temperature (14%)
Alrasheed *et al* 2016	92%	78.7%	Pharmacy (source), friends, relatives	amoxicillin, ciprofloxacin penicillin, metronidazole tetracycline, .amoxicillin clavulanate,streptomycin, erythromycin, doxycycline cephalosporins, trimethoprim, gentamicin	Cough Cold Sore throat Fever Pneumonia
Alrasheed 2017	96.3%/151	NR	Pharmacy, previous experience with the antibiotic	NR	Long waiting time to see a doctor, illness not considered serious enough to see a doctor, cold, sore throat, chest infection
Al-Shibani *et al* 2017	1974/2109(93.5 %)	51%	Pharmacy ,relatives	NR	Bacterial Infections

NR-not reported

APPENDIX 3 (continued) Studies of self-medication with antibiotics (SMA) in Saudi Arabia

Study	Number of respondents/ response rate	Prevalence of SMA (%)/	Source of antibiotics or information	Class of antibiotics reported	Indications for antibiotic use
Arwa *et al* 2018	NR	17.7%	Pharmacy	NR	Viral Infections
Belkina *et al* 2014	100%	48%	Pharmacy, friends, old stock at home	NR	Fever
Bin Nafisah *et al* 2017	(98.75%) 473 completed	48%	Pharmacy, old stock at home	NR amoxicillin-clavulanate	NR
El Zowalaty et 2016	1149/1310 (87.7%)	63.6%	Pharmacy	NR	Respiratory infections (55%) Miscellaneous use (26.9%) Gastrointestinal infections (6.6%)
Elberry *et al* 2012	(NR) 199 completed	NR	NR	azithromycin, cefuroxime, cefixime amoxicillin-clavulanate	Upper respiratory tract infections
Emeka *et al* 2014	489/607 (80.6%)	100%	Physicians, Pharmacy advertisements, Friends, previous experience	amoxicillin, amoxicillin-clavulanate cefazolin, cefaclor , gatifloxacin, ofloxacin ampicillin, erythromycin clarithromycin ,azithromycin, metronidazole, tetracycline	Cold Sore throat Acne Prophylaxis
Hajjar *et al* 2017	(NR) 400 completed	45.5%	Physician, Pharmacy, old stock at home Internet, media, friends and family, News and magazines	NR	Upper respiratory tract infections
Harakeh *et al* 2015	(NR) 1042 completed	49%	Physician, internet, medical textbooks	NR	Upper respiratory tract infections
Khalil *et al* 2013	(NR) 987 completed	64.5	Pharmacy, home, friend, internet	amoxicillin amoxicillin-clavulanate clindamycin	Dental pain

APPENDIX 4a

Life Expectancy at Birth in Saudi Arabia, 1980-2050

Year	Male	Female	Total
1980-1985	63.3	66.8	64.9
1985-1990	66.4	69.6	67.9
1990-1995	68.3	72.0	69.9
1995-2000	70.1	73.7	71.6
2000-2005	71.6	75.1	73.1
2005-2010	72.8	76.4	74.3
2010-2015*	73.8	77.5	75.4
2015-2020*	74.8	78.5	76.4
2020-2025*	75.9	79.4	77.4
2025-2030*	76.9	80.2	78.3
2030-2035*	77.9	81.0	79.3
2035-2040*	79.0	81.7	80.2
2040-2045*	80.0	82.4	81.0
2045-2050*	80.9	83.0	81.8

APPENDIX 4b

Age group distribution in Saudi Arabia 1980-2050

	Population by age group (%)			
Year	0-4	5-14	15-64	65+
1980	18.5	25.9	52.6	3.0
1985	17.4	25.3	54.7	2.6
1990	16.8	25.7	54.8	2.7
1995	14.1	26.9	56.3	2.6
2000	13.9	24.5	58.1	3.5
2005	11.4	22.9	62.6	3.1
2010	11.1	19.6	66.3	3.0
2015	9.6	18.7	68.7	3.0
2020	8.4	17.3	70.3	4.1
2025	6.5	16.3	71.7	5.4
2030	5.3	13.9	73.6	7.2
2035	5.1	11.2	74.2	9.5
2040	5.4	9.90	72.6	12.1
2045	5.5	10.0	69.1	15.4
2050	5.4	10.5	65.7	18.4

Source: United Nations, World Population Prospects:

http://esa.un.org/unpd/wpp/unpp/panel_indicators.htm