A STUDY ON THE PREVALENCE OF CLOSTRIDIUM DIFFICILE INFECTION AND ASSOCIATED RISK FACTORS IN LARGE HOSPITAL SETTINGS IN KOTA KINABALU, SABAH

NUR NASHYIROH IZAYATI BINTI MASTOR

THESIS SUBMITTED IN FULLFILLMENT FOR THE DEGREE OF MASTER OF SCIENCE

FACULTY OF MEDICINE AND HEALTH SCIENCE

UNIVERSITI MALAYSIA SABAH

2018

UNIVERSITI MALAYSIA SABAH

BORANG PENGESAHAN STATUS TESIS

JUDUL: **A STUDY ON THE PREVALENCE OF CLOSTRIDIUM DIFFICILE INFECTION AND ASSOCIATED RISK FACTORS IN LARGE HOSPITAL SETTINGS IN KOTA KINABALU, SABAH**

IJAZAH: SARJANA SAINS PERUBATAN

Saya **NUR NASHYIROH IZAYATI BINTI MASTOR**, Sesi **2016-2018**, mengaku membenarkan tesis Sarjana ini disimpan di Perpustakaan Universiti Malaysia Sabah dengan syarat-syarat kegunaan seperti berikut:-

1. Tesis ini adalah hak milik Universiti Malaysia Sabah
2. Perpustakaan Universiti Malaysia Sabah dibenarkan membuat salinan tujuan pengajian sahaja.
3. Perpustakaan dibenarkan membuat salinan tesis ini sebagai bahan pertukaran antara institusi pengajian.
4. Sila tandakan (/):

☐	SULIT (Mengandungi maklumat yang berdarjah keselamatan atau Kepentingan Malaysia seperti yang termaktub di dalam AKTA RAHSIA 1972)
☐	TERHAD (Mengandungi maklumat TERHAD yang telah ditentukan oleh organisasi/badan di mana penyelidikan dijalankan)
☑	TIDAK TERHAD

PERPUSTAKAAN
UNIVERSITI MALAYSIA SABAH

Disahkan oleh,

NORAZLYNNE MOHD JOHAN @ JA[illegible]LYNE
PUSTAKAWAN
UNIVERSITI MALAYSIA SABAH

NUR NASHYIROH IZAYATI BT MASTOR
MM1521003T

(Tandatangan Pustakawan)

Tarikh : 4 DISEMBER 2018

DR. MOHAMMAD ZAHIRUL HOQUE
Associate Professor
Faculty Of Medicine & Health Sciences
University Malaysia Sabah
Malaysia
MMC FULL Reg. No.53636

(Assoc. Prof. Dr Mohammad Zahirul Hoque)
Penyelia Utama

(Assoc. Prof. Dr Shamsul Bahari bin Shamsudin)
Penyelia Bersama

Dr. Shamsul Bahari Shamsudin (PhD)
Associate Professor
Faculty of Medical & Health Sciences
Universiti Malaysia Sabah

DECLARATION

I hereby declare that the work in this thesis is my own except for quotation, equations, summaries and references which have been duly acknowledge.

22 NOV 2018

Nur Nashyiroh Izayati binti Mastor

MM1521003T

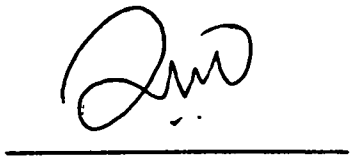
CERTIFICATION

NAME	**: NUR NASHYIROH IZAYATI BINTI MASTOR**
MATRIC NO	**: MM1521003T**
TITLE	**: A STUDY ON THE PREVALENCE OF CLOSTRIDIUM DIFFICILE INFECTION AND ASSOCIATED RISK FACTORS IN LARGE HOSPITAL SETTINGS IN KOTA KINABALU, SABAH**
DEGREE	**: MASTER OF SCIENCE (MEDICAL SCIENCE)**
VIVA DATE	**: 9 NOVEMBER 2018**

CERTIFIED BY;

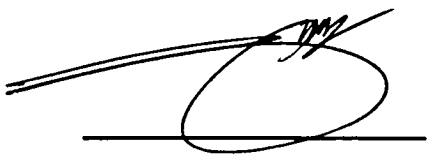
SUPERVISOR

Assoc Prof. Dr. Mohammad Zahirul Hoque — Signature



CO-SUPERVISOR

Assoc. Prof. Dr. Shamsul Bahari bin Shamsudin — Signature



ACKNOWLEDGEMENT

I would like to convey my deepest gratitude to Allah (Azza Wa Jalla) for the strength along my journey in making my Master studies in Universiti Malaysia Sabah a possible.

The completion of undertaking could have not been possible without the participation and assistance of so many people whose name may not all be enumerated. Their contributions are sincerely appreciated and gratefully acknowledge.

Many thanks to my beloved parents, husband and family for being supportive and allowing me to be distracted at home. Nobody has been more important to me in the pursuit of this Master studies than the members of my family.

To my mentors Assoc. Prof. Dr Mohammad Zahirul Hoque and Assoc. Prof. Dr Shamsul Bahari bin Shamsudin, thank you for all the valuable guidance and opportunities I was given to conduct this study and also provided me with tools that I needed to choose the right direction.

I am also grateful to those who I have been working during this and other related project or studies. Queen Elizabeth Hospital and Women and Children Likas Hospital staff and not to forget the staff of Universiti Malaysia Sabah.

To all relatives, friends and others who in one way or another shared their support either morally, financially and physically, thank you.

Above all, to the great Almighty, the author of the knowledge and wisdom and for His countless love.

We thank you.

Nur Nashyiroh Izayati binti Mastor

22 NOV 2018

ABSTRACT

Clostridium difficile is a gram positive anaerobic bacterium and has emerged as a global public health problem especially in hospitalized patients. The prevalence rate of *Clostridium difficile* infection (CDI) varies among different regions of the world. *C. difficile* can be found in soil, water and faeces and it is naturally present in normal healthy human intestine. CDI is transmitted via faecal-oral route and by contact with the stool of infected patient or through healthcare workers. There have been only a few studies reported from Asia Pacific countries including Malaysia. Antibiotic is the predominant risk factor for CDI other than advanced age, comorbidities and length of hospitalization. The aim of the present study was to determine the prevalence and risk factor associated with CDI among hospitalized patients in a large tertiary hospital in Sabah, Malaysia. A total number of 1475 stool suspected for CDI from two hospital in Kota Kinabalu Sabah were tested with two commercial rapid diagnostic test kits; (1) C. DIFF QUIK CHEK COMPLETE (Alere, Techlab, USA) and (2) DUO TOXIN A&B (VEDA Lab, France) according to manufacturer's protocol. Adult and children stool samples were taken from Queen Elizabeth Hospital and Women and Children Hospital Kota Kinabalu Sabah Malaysia from January 2016 to May 2018. The patient's age range from 1 to 97 years old. The demographic data and other clinical information were obtained from hospital medical record and analysed using a standard questionnaire base on Bauer MP et al (2011). In this present study, we found that the overall prevalence of adult CDI was 4.6% (57/1226). There were 35.7% (20/56) of the positive adult CDI patients belong to more than 65 years of age group. Results from C. DIFF QUIK CHEK COMPLETE (Alere,Techlab,USA) showed 14 positive cases were either antigen or toxin positive. The rate of antigen positivity was 17.5% and toxin positivity was 82.5%. Stool tested with DUO TOXIN A&B test kit indicated 57.9% toxin B positivity, 10.5% toxin A&B and 1.8% toxin A. Out of examined patients 56.8% were male and 87.7% of the study population had prior history of antibiotic uses and comorbidity was reported 64.1%. Recurrence rate was 14.3%. For children data, we observed 80 of the 249 stool samples were positive either *C. difficile* antigen and/or toxin. The overall incidence was 32.1%.The rate of antigen positivity was 86.25% and toxin positivity was 13.75%. The median age of the studied children was 6 years. Similar with adult CDI patients, children female patients are more common diagnosed with CDI in our study compare to male children. Most of the test positive children were colonized with non-toxigenic *C. difficile*. The recurrence rate was 11.25%. In conclusion, the total prevalence was 9.3% and we observed low incidence of toxigenic *C. difficile* among hospitalized adult and children patients from the two hospitals during the study period. The findings of this study suggest that long-term surveillance is needed to understand the epidemiology of the dangerous emerging pathogen and control the infections in hospital and community.

Keywords: *Clostridium difficile*, Prevalence, Diagnostic test kit

ABSTRAK

KAJIAN TENTANG PREVALENS JANGKITAN CLOSTRIDIUM DIFFICILE DAN FAKTOR RISIKONYA DI HOSPITAL SEKITAR KOTA KINABALU SABAH, MALAYSIA

Clostridium difficile ialah gram positif anaerobik bakteria dan telah menjadi masalah kesihatan global terutamanya kepada pesakit yang dimasukkan ke wad hospital. Kadar prevalen/kelaziman jangkitan Clostridium difficile (CDI) berbeza di kawasan yang berlainan di dunia. C.difficile boleh didapati di dalam tanah, air serta najis dan ia hadir secara semula jadi dalam usus manusia biasa yang sihat. Penularan penyakit ini adalah melalui pendedahan tinja pesakit yang dijangkiti ke mulut (faecal oral route) atau sentuhan langsung melalui pekerja di hospital. Hanya terdapat beberapa kajian yang dilaporkan dari negara-negara Asia Pasifik termasuk Malaysia. Antibiotik adalah faktor risiko utama untuk CDI selain lanjut usia, komorbiditi dan tempoh rawatan yang lama di wad hospital. Tujuan kajian ini adalah untuk menentukan prevalen/kelaziman penyakit CDI dan faktor risikonya di hospital sekitar Kota Kinabalu Sabah Malaysia. Sebanyak 1475 spesimen tinja disyaki menghidap CDI dari dua buah hospital di Kota Kinabalu Sabah telah diuji dengan menggunakan dua jenis kit ujian diagnostik komersial; (1) C. DIFF QUIK CHEK LENGKAP (Alere, Techlab, Amerika Syarikat) dan (2) DUO TOKSIN A & B (VEDA Lab, Perancis) mengikut protokol kilang pengeluar. Sampel tinja pesakit dewasa dan kanak-kanak telah diambil dari Hospital Queen Elizabeth dan Hospital Wanita dan Kanak-Kanak Likas Kota Kinabalu Sabah Malaysia. Umur pesakit adalah dalam lingkungan 1 sehingga 98 tahun. Data demografi dan maklumat klinikal pesakit telah diperolehi daripada rekod kesihatan pesakit dan dianalisis menggunakan asas selidik berdasarkan Bauer MP et al (2011). Dalam kajian ini, kami mendapati prevalen keseluruhan pesakit dewasa yang dijangkiti CDI adalah 4.6% (57/1226). Terdapat 35.7% (20/56) daripada pesakit tersebut adalah daripada golongan mereka yang berumur lebih daripada 65 tahun. Dengan menggunakan kit ujian C. DIFF QUIK CHEK COMPLETE (Alere, Techlab, Amerika Syarikat), 14 kes adalah positif sama ada antigen atau toksin. Kadar antigen positif adalah 17.5% dan toksin adalah 82.5%. Manakala sampel tinja yang diuji dengan kit ujian DUO TOKSIN A & B menunjukkan 57.9% adalah toksin B positif, 10.5% toksin A & B dan 1.8% toksin A. Daripada bilangan pesakit, 56.8% adalah lelaki dan 87.7% daripada populasi kajian mempunyai pendedahan antibiotic terdahulu dan komorbiditi dilaporkan 64.1%. Kadar berulang CDI pesakit adalah 14.3%. Untuk data kanak-kanak, kami menadapati 80 daripada 249 sampel najis adalah CDI positif antigen dan / atau toksin. Insiden keseluruhan adalah 32.1%. Kadar antigen positiviti adalah 86.25% dan toksin adalah 13.75%. Median umur kanak-kanak adalah 6 tahun. Pesakit kanak-kanak perempuan adalah lebih tinggi didiagnosis dengan CDI dibandingkan dengan kanak-kanak lelaki. Kebanyakan kanak-kanak yang positif adalah bukan toxigenic C. difficile. Kadar berulang adalah 11.25%. Secara kesimpulannya, insiden secara keseluruhan adalah 9.3% dan CDI prevalens adalah rendah di kalangan pesakit dewasa dan kanak-kanak di dua buah hospital sepanjang tempoh kajian dijalankan. Hasil kajian ini menunjukkan bahawa pengawasan masa jangka panjang adalah penting untuk memahami epidemiologi patogen baru yag berbahaya bagi mengawal jangkitan penyakit ini di hospital dan komuniti.

Kata kunci: Clostridium difficile, Prevalens, Kit diagnostic

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAD	Antibiotic Associated Diarrhoea
Ag	Antigen
CAA	Community Acquired Diarrhoea
CA-CDI	Community acquired *Clostridium difficile* infection
CDAD	*C. difficile*-associated-diarrhoea
CDI	*Clostridium difficile* infection
EIA	Enzyme Immunoassay
FMT	Fecal Microbiota Transplant
GDH	Glutamate Dehydrogenase
HAI	Hospital Acquired Infection
HDW	High Disease Ward
HRP	Horseradish peroxidase
ICU	Intensive Care Unit
IgA	Immunoglobulin A
IgG	Immunoglobulin B
IgM	Immunglobulin M
LCF	Long term care facility
PaLoc	Pathogenicity Locus
PCR	Polymerase Chain Reaction
SCr	Serum Cretinine
WBC	White Blood Cell Count
WCH	Women and Children Hospital
WHO	World Health Organization
QEH	Queen Elizabeth Hospital

LIST OF PHOTOS

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Introduction

Clostridium difficile (*C. difficile*) is a gram-positive bacilli, it forms spore and its toxigenicity may cause symptomatic illnesses such as diarrhoea and severe diseases pseudomembranous colitis and megacolon (Rupnik *et al.*, 2009). It is widely known as antimicrobial-associated infectious diarrhoea in hospitalized patients in economically developing nations due to increased use of the broad-spectrum antibiotic. *C. difficile* can be found ubiquitous in soil, water and faeces and it is naturally present in the average healthy human intestine. Transmission is via the faecal-oral route and by contact with the stool of an infected patient or through healthcare workers.

Clostridium difficile infection (CDI) can be symptomatic and asymptomatic. Two main glucosyltransferases toxins mediate *C. difficile* pathogenicity; toxin A (enterotoxin) and B (cytotoxin) (Kelly and LaMont., 2008). These toxins can be found in pathogenicity locus (PaLoc) of 19.6 kb encoded tcdA and tcdB within the chromosome of *C. difficile*. Some *C. difficile* may have another binary toxin CDT which encoded by the genes cdtA and cdtB located in the CDT locus (CdtLoc) (Martinez *et al.*, 2017). Many studies have been done to analyze and comprehend the toxin effect of *C. difficile*. Asymptomatic colonization of these bacteria can also occur with toxigenic strains. Thus, the confirmation of CDI and its detection is through the stool samples with the presence of diarrhoea symptoms.

1.2 Research Background

Since CDI outbreaks occurred in Quebec, Canada in 2003, *C. difficile* becomes common in the healthcare environments because of their link to antibiotic therapy. Since then, these bacteria which do not need oxygen to live and reproduce has been widely studied and explored by various scientists in North America and also in Europe.

The numbers of *C. difficile* cases has become significantly increasing significant and the healthcare has been spending almost 1 billion annually in the United States (Kyne *et al.*, 2002). The rising cost might be due to the better

detection method that contributed to the increase reported *C. difficile* cases and also a high frequency of antibiotic usage. In addition to this, since the frequency of disease has increased, the hospital and healthcare facilities become contaminated with *C. difficile* spore making it is easy to affect those who are susceptible.

Many infection control program and disease prevention strategies have been introduced to control the spread of CDI disease such as antibiotic stewardship. This infection control program and disease prevention are mainly to balance between infection control and antibiotic management, at the same time to achieve the optimal clinical outcomes. It is also to decrease adverse drugs events and minimize the development of antibiotic resistance. This creates huge issues for antibiotic stewardship and can lead to increasing antibiotic resistance.

The first true antibiotic 'penicillin' was discovered in 1928 by Sir Alexander Fleming and treated many types of bacterial infections. However, the antibiotic drug has been abused through the improper use of antibiotic by taking a longer duration of antibiotic than necessary and unnecessary prescription of antibiotics by clinicians. The problem arises when *C. difficile* treatment can impact treatments of other diseases. Patient prescribed with an antibiotic for a primary infection increase their susceptibility to CDI and must discontinue and replace with antibiotic specific for *C. difficile* treatment. The possibility for the patient sick again will occur due to the primary infection is not fully cured. The spores present in the gastrointestinal tract have become resistant to antibiotics also possibly contribute to recurrent disease infection and the chance of getting *C. difficile* relapse cycle (Robert and Vincent., 2014; Johnson *et al.*, 1989) (Figure 1).

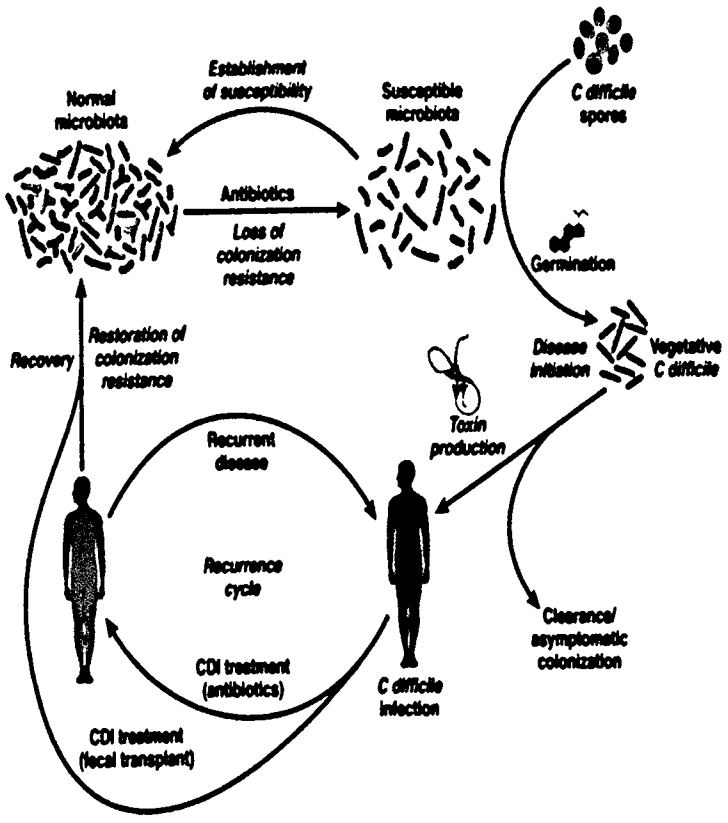


Figure 1.1 : Cycle of *Clostridium difficile* infection (CDI)
Source : Robert and Vincent., (2014)

In another study, recurrence of CDI has been identified by the European Society of Clinical Microbiology and Infectious Disease (ESCMID) as the most critical of problem in the treatment of CDI (Bauer *et al.*, 2009). The rate of recurrence CDI reported was 20% by the first episode, 45% after recurrence and 65% after two or more recurrences (Cohen *et al.*, 2010). According to DuPont., (2011), recurrence appears to be related to the merging of many components such as failure to re-establish the normal microflora in the intestine, the existance of *C. difficile* spore in the intestine and a sub-optimal host immune response towards the pathogenic organism and its toxin.

The rising incidence of CDI leads to the higher mortality associated with *C. difficile* virulence and host vulnerability. One study showed that discontinuation of CDI antibiotic and lower immune response to *C. difficile* toxin are the factors that increase CDI recurrent (Kyne *et al.*, 2001).

Kamboj *et al.*, (2011) did a study using molecular typing to compare the types of *C. difficile* isolated that result in the occurrence of initial and recurrent episodes in adult CDI. They found that 88% of recurrence CDI patients are infected with the same strain of *C. difficile* within eight weeks. The same *C. difficile* strain was also found with patients that had second episodes of more than eight weeks with 65 percentages. Figueroa *et al.*, (2012) discovered the same findings while Polage *et al.*, (2012) reported diarrhoea after an initial episode of CDI may not be CDI.

There were observed evidence of publication and studies in Asia on CDI and its associated risk factor including its molecular studies. The probability for circulating strain from another region can spread to Asian region is present. Some ribotypes are hypervirulent and are spreading worldwide suh as RT 027, the significant ribotypes in North America, has been reported sporadically in Hong Kong, Japan, South Korea, Singapore and recently, in China (Miller *et al.*, 2010). Another study reported most common ribotypes in East Asia are RT017, 018, 014, 002 and 001, which are also among the top ten most commonly found ribotypes in Europe (Putsathit *et al.*, 2015). By far, there are no significant findings on the hypervirulent strain 027 or 078 in Asia.

Collins *et al.*, (2017) mentioned in his findings that toxin positive B ribotype 017 believed to be originated from the Asian region. Poor awareness among Asians physicians, patients with CDI was incorrectly diagnosed and underdiagnosed resulting in rare prevalence data report in Asia especially in Southeast Asia (Mavros *et al.*, 2012 and Warren *et al.*, 2012). It has also been found that limited clinical information and small sample size in Asia caused CDI study not as widely carried out as the USA and Europe.

Previous studies were done by Nienke *et al.*, (2017) on the prevalence of CDI in Asia using meta-analysis method. They observed the highest prevalence was from East Asia (19.5%) in comparison to South Asia (10.5%) and the Middle East (11.1%). They concluded the prevalence of CDI cases in Asia is concurrent with those has been reported from Western countries where the pool incidence rate of this disease from Asia was 5.3 per 10,000 patient days.

It has been well known that most of the previous studies suggested that the primary risk factor for CDI is antibiotic exposure, extreme age and prolonged hospitalization (Putsathit *et al.*, 2017). The strongest predominant risk factor is the unnecessary antibiotic treatment or redundant therapy result in using broad-spectrum antibiotic by the patient in most Asian countries (Bhatia and Narain., 2010). The impacts not mainly limit to the individual patient level but increase hospital expenses. The symptoms of CDI can be detected on the first day of antibiotic administered up to 8 weeks after termination regardless of how many types antibiotic is given to the patients (Hassan *et al.*, 2012).

The antibiotic that is frequently reported to be the cause of CDI are antibiotics such as clindamycin, cephalosporins and fluoroquinolones that suppress the healthy microflora in the gastrointestinal tract and trigger *C. difficile* growth (Sliming and Riley,. 2014; Hensgens *et al.*, 2012). The treatment of CDI depends on the severity of symptoms and disease. Older studies showed that metronidazole is widely prescribed and become the drug of choice for first-line antibiotic treatment for CDI. Vancomycin is the option for moderate to severe CDI cases.

C. difficile resistance towards antibiotic is widely discussed although the resistance mechanism is still unclear. Broad spectrum antibiotic usage increases bacterial resistance and the treatment of CDI become ineffective and increases in severity as the alterations of the antibiotic target sites occur (Tian *et al.*, 2016).

Elderliness is known to be associated with CDI. Those aged more than 65 years old prone to get CDI disease due to their lower self-immunity and also comorbidities (Hassan *et al.*, 2012; Nienke *et al.*, 2017). A prospective population-based analysis in Sweden indicated CDI rate was ten times higher in individual older than 65 years (Latisha H and Jimmy D., 2011).

C. difficile spore-formed can survive and adapt to the surrounding, especially in the hospital and healthcare facility. The spore has a versatile genetic content which makes it ubiquitous in the environment, hard to eliminate and become broad resistance to the antibiotic for treatment and prevention. Patients in the hospital are exposed to the spore therefore the length of hospitalization is also one of risk factor (Greta *et al.*, 2017; and Elsevier *et al.*, 2015). Intensive care units, surgical and internal medicine departments were observed to be the highest frequencies of antibiotic treatment in the hospital (Elsevier *et al.*, 2015; Florian *et al.*, 2017).

Some studies mentioned that comorbidities and proton pump inhibitor usage are the confounding factors for CDI. The presence of comorbidities lower level of individual body immunity thus intestinal resistance is low and easy to be proliferated by *C. difficile*. Previous studies indicated that inflammatory disease, diabetes mellitus and renal failure are the appropriate populations for interventional studies of CDI screening (Furuya *et al.*, 2015). Cancer and HIV patients tend to predispose to CDI due to immunological failures risk factors (Cecilia *et al.*, 2014).

More frequent and severe outbreaks of CDI of which *C. difficile* has started to spread to a new group of the population with no risk factor since a decade ago (Monnier *et al.*, 2014). Recent studies showed that the susceptibility of *C. difficile* towards antibiotic treatment in particular metronidazole had been decreased (Patrizia., 2016). The recurrence of infections and failure in the treatment open other therapy options for CDI such as rifamycins and fidaxomicin (Viswanathan *et*

al., 2010) and the latest include fecal microbiota transplantation (FMT) for the disease that is resistant to vancomycin.

1.3 Objectives of the Study

1.3.1 General Objectives

It should be noted that the scope of this study is to investigate the prevalence of *C.difficile* infection (CDI) in two large hospitals setting in Kota Kinabalu, Sabah Malaysia and its associated risk factor. The objective of this study is:

1) To determine the prevalence of CDI cases in large hospital settings in Kota Kinabalu, Sabah Malaysia.

2) To determine the current evidence and risk factors among adult and children of CDI patients such as age, antibiotic usage and length of hospitalization.

1.3.2 Specific Objectives

The specific objectives of this study are:

a) To determine the prevalence of CDI cases in two hospitals in Kota Kinabalu, Sabah Malaysia.

b) To identify the risk factors that contributes to CDI (Antibiotic usage, ward types and age) among the respondents.

c) To investigate the significant difference of CDI cases among the different age group and gender.

d) To determine the association of CDI cases with age of the respondents.

e) To investigate the association of CDI cases with other confounding factors with CDI positive respondents.

1.4 The significance of the study

The result of this study will help in defining the prevalence of CDI cases in Kota Kinabalu Sabah Malaysia and also identify its contributing risk factor from the subject population. In this study, 1475 suspected *C. difficile* stool samples from the

warded patient of Women and Children Hospital and Queen Elizabeth Hospital Kota Kinabalu, Sabah Malaysia were included.

The epidemiology of *C. difficile* is changing and the rates of CDI and disease severity are increasing with significant morbidity and mortality has been observed in recent cases involving an epidemic strain. Traditionally, *C. difficile* is a common hospital-acquired infectious disease and has been re-emerged in recent years with greater morbidity and mortality.

Misuse of antibiotic could lead to resistance creating a global antibiotic resistance crisis in 20th centuries. Widespread unregulated antibiotic use and inappropriate prescribing in South East Asian countries indicate that CDI could be widespread in these regions where close observation is currently lacking (Popchai et al., 2015). It is found that the antibiotic usage becomes prominent not only in the USA and European country but also in Asia (Putsahit *et al.*, 2017).

The treatment and prevention of CDI such as antimicrobial stewardship and alternative therapies become complicated by the non-stop emergence of new phenotypic and genotypic traits. Adherence of the local guidelines for the antibiotic prescription is vital to ensure the antibiotic with the narrowest spectrum is being used.

Although *C. difficile* has always been a cause of diarrhoeal disease in hospitalized patients, the rates of community-associated diarrhoea disease have increased. In Asia, several studies showed the uprising of CDI cases not only among hospitalized patient but also in the community. The patients become lack of 'classical' risk factor; antibiotic exposure, recent hospitalization and advanced age. The diversity of *C. difficile* strain evolves rapidly due to widely genetic transfer between these bacteria with other bacterial species.

The recent analysis of *C. difficile* with the use of whole-genome sequencing suggests that many cases of CDI were genetically distinct and not transmitted by recent symptomatic carriers in the hospital environment (Eyre *et al.*, 2013). Therefore, long-term surveillance is essential to understand the epidemiology of this dangerous emerging pathogen to control the spreading of infections not only in the hospital but the community as well.

In the Asian region, in order to slow the development of antibiotic resistance, increasing laboratory capacity in the region as well as improving surveillance should be seen as essential in preventing unnecessary morbidity and mortality CDI cases.

1.5 Definition of Key Terms

To understand and clarify the terms used in the study, the following are hereby defined:

1.5.1 Conceptual Definition

a. Prevalence

Prevalence (or to be more correct, prevalence proportion an sometimes point of prevalence) gives a figure for a factor at a single point in time (Jekel *et al.*, 2001).

b. *Clostridium difficile* Infection (CDI)

Three times or more stool passed (watery, loose or unformed) within 24 hours (McFarland., 2008; Thielman and Wilson., 2005; Hempel *et al.*, 2012; Bauver and Dissel., 2009).

c. Hospital Acquired Infections (HAIs)

An infection acquired in the hospital more than 24 hours after admission and is admitted other than that infection. An infection is occurring in a patient in a hospital or other healthcare facility in whom the infection was not present or incubating at the time of admission. Also known as nosocomial infection (Horan *et al.*, 2008).

d. Antibiotic-associated diarrhoea (AAD)

Diarrhoea occurs in association with antibiotic administration. It happens either during or after taking antibiotics (Susan., 2007).

e. Recurrent CDI

Recurrence was defined as an episode of CDI occurring within eight weeks after the onset of a previous infection, provided the symptoms from the earlier episode resolved with or without therapy (Aslam *et al.*, 2005; Greta Roncarati *et al.*, 2017). Recurrent CDI occur either by relapsing with the original infection strain or re-infection with a new *C.difficile* strain.

REFERENCES

Aberra FN, Gronczewski CA, Katz JP. (2012) *Clostridium difficile* Colitis. Medscape Reference: Drugs, Diseases and Procedures.

Ackermann G, Thomalla S, Ackermann F, Schaumann R, Rodloff AC, Ruf BR. (2005) Prevalence and characteristics of bacteria and host factors in an outbreak situation of antibiotic-associated diarrhoea. *J Med Microbiol*, 54: 149-153.

Adrián Martínez-Meléndez, Adrián Camacho-Ortiz, Rayo Morfin-Otero, Héctor Jesús Maldonado-Garza, Licet Villarreal-Treviño, Elvira Garza-Gonzále. (2017) Review: Current knowledge on the laboratory diagnosis of infection. *World J Gastroenterol*, 23(9): 1552-1567.

Adlerberth, I. Huang, H.; Lindberg, E. Aberg, N. Hesselmar, B. Saalman, R. Nord, C.E. Wold, A.E. Weintraub, A. (2014) Toxin-producing *Clostridium difficile* strains as long-term gut colonizers in healthy infants. *J. Clin. Microbiol*, 52, 173–179.

Aju Daniel and Alwyn Rapose. (2015) The evaluation of *Clostridium difficile* infection (CDI) in a community hospital. *J Infect Public Health*, 8(2):155-60. doi: 10.1016/j.jiph.2014.08.002. Epub 2014 Oct 6.

Alcalá L, Reigadas E, Marín M, Martín A, Catalán P, Bouza E, Spanish *Clostridium difficile* Study Group. (2015) Impact of clinical awareness and diagnostic tests on the underdiagnosis of *Clostridium difficile* infection. *Eur J Clin Microbiol Infect Dis*, 34:1515–25.

Albert MJ, Faruque AS, Faruque SM, Sack RB, Mahalanabis D. (1999) Case–control study of enteropathogens associated with childhood diarrhoea in Dhaka, Bangladesh. *J Clin Microbiol*, 37(11):3458-3464.

Alberto Co ´zar-Llisto´. Antonio Ramos-Martinez. Javier Cobo. (2016). Review: *Clostridium difficile* Infection in Special High-Risk Populations. *Infectious Disease Therapy*, 5:253-269.

Alvarez-Perez S, Blanco J.L, Martinez-Nevado E, Pelaez T, Harmanus C, Kuijper E and Garcia M.E. (2014) Shedding of *Clostridium difficile* PCR ribotype 078 by zoo animals, and report of unstable metronidazole-resistant isolate from a zebra foal (Equus quagga buechelli). *Veterinary Microbiology* 169: 218-222.

Al-Jashaami L.S and Dupont H.L.(2016) Management of *Clostridium difficile* Infection. Gastroenterology and Hepatology. Vol 12(10).

Al-Thani A.A, Hamdi W.S, Al-Ansari N.A and Doiphode S.H. (2014) Polymerase chain reaction ribotyping of *Clostridium difficile* isolates in Qatar: a hospital-based study. *BioMed Central Infectious Diseases*, 14:502.

Andrew Ofasu.(2016) Review Article: *Clostridium difficile*: A review of current and emerging therapies. *Annals of gastrology* , 29,147-159.

Anna M. Seekatz, Johannes Aas, Charles E. Gessert, Timothy A. Rubin, Daniel M. Saman, Johan S. Bakken, and Vincent B. Young. (2014). Recovery of the Gut Microbiome following Fecal Microbiota Transplantation. mBio; 5(3): e00893-14.

Aronsson B, Granstrom M, Mollby R, Nord CE. (1985) Serum antibody response to Clostridium difficile toxins in patients with *Clostridium difficile* diarrhoea. Infection. 13:97–101.

Arvand M, Hauri AM, Zaiss NH, Witte W, Bettge-Weller G. *Clostridium difficile* ribotypes 001, 017, and 027 are associated with lethal *C. difficile* infection in Hesse, Germany. *Euro Surveill.* 2009; 14:pii: 19403.

Asha NJ, Tompkins D, Wilcox MH. (2016) Comparative analysis of prevalence, risk factors, and molecular epidemiology of antibiotic- associated diarrhea due to *Clostridium difficile*, *Clostridium perfringens*, and *Staphylococcus aureus*. *J Clin Microbiol* , 44: 2785-2791.

Ayse Karaaslan, Ahmet Soysal, Nurhayat Yakut, Gulsen Akkoç, Sevliya Ocal Demir, Serkan Atıcı, Nurver Ulger Toprak, Guner Söyletir and Mustafa Bakır. (2016) Hospital acquired *Clostridium difficile* infection in pediatric wards: a retrospective case–control study. SpringerPlus. 5:1329.

Barbut F, Mastrantonio P, Delmee M, Brazier J, Kuijper E, Poxton I. (2007) Prospective study of *Clostridium difficile* infection in Europe with phenotype and genotypic characterization of the isolates.*Clinical Microbial Infection* , 13;1048-1057.

Bassetti M, Villa G, Pecori D, Arzese A, Wilcox M. (2012) Epidemiology, diagnosis and treatment of *Clostridium difficile* infection. *Expert Rev Anti Infect Ther*, 10(12):1405-23.

Bartlett John G. Antibiotic-Associated Diarrhea.(1992) *Clinical Infectious Diseases*, Volume 15 (4), Pg 573–581.

Bauer MP, van Dissel JT. (2009) Alternative strategies for *Clostridium difficile* infection. Int *J Antimicrob Agents* ,33 Suppl 1:S51–6.

Bauer MP, Notermans DW, van Benthem BH, Brazier JS, Wilcox MH, Rupnik M, Monnet DL, van Dissel JT, Kuijper EJ.(2011) *Clostridium difficile* infection in Europe: a hospital-based survey. Lancet, 377(9759):63-73. doi: 10.1016/S0140-6736(10)61266-4.

Benson L, Song X, Campos J, Singh N.(2007) Changing epidemiology of *Clostridium difficile*-associated disease in children. *Infect Control Hosp Epidemiol*, 28: 12.33-1235.

Bhatia R, Narain JP. (2010) The growing challenge of antimicrobial resistance in the South-East Asia Region are we losing the battle? *Indian J Med Res*, 132:482–6. https://doi.org/10.4103/0971-5916.73313 PMID: 21149995.

Blakney R, Gudnadottir U, Warrack S, O'Horo J.C, Anderson M, Sethi A, Schmitz M, Wang J, Duster M, Ide E, Safdar N. (2015) The relationship between patient functional status and environmental contamination by *Clostridium difficile*: a pilot study. Springer-Verlag Berlin Heidelberg.

Blaich A, Frei R, Castellano C, Kiessling, Geschke A, Rentsch K.M, Egli A.(2017) Evaluation of two novel chemiluminescence immunoassays for the detection of *Clostridium difficile* glutamate dehydrogenase and toxin A&B. *Journal of Microbiological Methods* 135: 63-65.

Bloomfield L.E and Riley T.V. (2016) Epidemiology and Risk Factors for Community Associated *Clostridium difficile* Infection: A Narrative Review. *Infectious Disease Therapy*, 5:231-251.

Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, Stollman N, Rohlke F, Surawicz C. (2012) Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection.*Am J Gastroenterol*, 107(7):1079-87. doi: 10.1038/ajg.2012.60. Epub 2012 Mar 27.

Brecher S.M, Novak-Weekley S.M and Nagy E. (2013) Laboratory Diagnosis of *Clostridium difficile* Infections: There is Light at the End of Colon. *Clinincal Practice*. CID:57.

Burke K.E and Lamont J.T. (2014) Review: *Clostridium difficile* Infection: A worldwide disease. *Gut and Liver*. Vol 8 (1). pp 1-6.

Burnham CA, Carroll KC. (2013). Diagnosis of *Clostridium difficile* infection: an ongoing conundrum for clinicians and for clinical labo- ratories. *Clin Microbiol Rev* 26:604–630.

Cecília L. Costa'Correspondence information about the author Cecília L. CostaEmail the author Cecília L. Costa, Carlos Quesada-Gómez, Cibele B. Mano de Carvalho, Rafael H. González, Markus A. Gifoni, Ronaldo A. Ribeiro, Gerly Anne de Castro Brito.(2014) Community-acquired diarrhea associated with *Clostridium difficile* in an HIV-positive cancer patient: first case report in Latin America. *International Journal of Infectious Disease*. Volume 26, Pg 138–139

Chang SC, Su CH, Chou WH, Hwang KP, Chuang YC, Chou MY, Leu HS, Wang FD, Wang JT, Wang LS, et al: Epidemiology of nosocomial *Clostridium difficile* disease in Taiwan. Taiwan Epidemiology Bulletin 2009, 25(3):163–177.

Chang JY, Antonopoulos DA, Kalra A. (2008) Decreased diversity of the fecal microbiome in recurrent *Clostridium difficile*-associated diarrhea. *J Infect Dis*, 197:435–438.

Chandrabali Ghose. *Clostridium difficile* infection in the twenty-first century. *Emerging Microbes and Infections* (2013) 2, e62; doi:10.1038/emi.2013.62 ?2013 SSCC.

Cheng J.W., Xiao M., Kudinha T., Xu Z.P., Sun L.Y., Hou X. The role of glutamate dehydrogenase (GDH) testing assay in the diagnosis of *Clostridium difficile* infections: a high sensitive screening test and an essential step in the proposed laboratory diagnosis workflow for developing countries like China. PLoS One. 2015;10:e0144604.

Chen S, Gu H, Sun C, Wang H and W J. Rapid detection of *Clostridium difficile* toxin and laboratory diagnosis of *Clostridium difficile* infections. 2016.

Chitnis AS, Holzbauer SM, Belflower RM et al.,Epidemiology of community associated *Clostridium difficile* infection,2009 through 2011. *JAMA Intern Med* 2013;173:1359-1367.

Cindy Lam, Alison McClean, Erika Koeck, Lei Ang, Prenilla Naidu, Ken Wagner, Kingsley Donkor. (2016) Investigation of Matrix Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF-MS) for detection of Clostridium difficile toxin A and B from stools. *Journal of Experimental Microbiology and Immunology* (JEMI). Vol. 20: 1 – 6

Claire Kenneally, Jamie M. Rosini, Lee P. Skrupky, Joshua A. Doherty, James M. Hollands, Emily Martinez, Wendi McKenzie, Theresa Murphy, Jennifer R. Smith, Scott T. Micek, Marin H. Kollef. (2007) Analysis of 30-Day Mortality for *Clostridium difficile*-Associated Disease in the ICU Setting. *Chest Journal*. Volume 132(2), Pages 418–424.

Claudia Slimings, Paul Armstrng, Wendy D, Ann L Bull, Lisa Hall, Karina JK, John Marquess. (2014) Increasing incidence of *Clostridium difficile* infection, Australia, 2011-2012. MJA, 200: 272–276doi: 10.5694/mja13.11153.

Clements AC, Magalhaes RJ, Tatem AJ, Paterson DL, Riley TV. (2010) *Clostridium difficile* PCR ribotype 027: assessing the risks of further worldwide spread. *Lancet Infect Dis*, 10(6):395-404.

Collins DA, Hawkey PM, Riley TV. (2013) Epidemiology of *Clostridium difficile* infection in Asia. *Antimicrobial Resistance and Infection Control.* 2:21.

Collins D.A and Riley T.V.(2016) Routine detection of *Clostridium difficile* in Western Australia. Anaerobe.37,34-37.

Collins DA, Gasem MH, Habibie TH, Arinton IG, Hendriyanto P, Hartana AP and Riley TV. (2017) Prevalence and molecular epidemiology of *Clostridium difficile* infection in Indonesia. *New Microbe and New Infect*, 18: 34-37.

Crobach MJT, Dekkers OM, Wilcox MH and Kuijper EJ. (2009) (ESCMID): Data review and recommendations for diagnosing *Clostridium difficile*-infection (CDI). European Society of Clinical Microbiology and Infectious Diseases. *Clinical Microbiology and Infection*, Volume 15(12).

Crogan NL, Evans BC. (2007)*Clostridium difficile*: an emerging epidemic in nursing homes. *Geriatr Nurs*, 28:161-4.

C. Eckert, A. Emirian, A. Le Monnier, L. Cathala, H. De Montclos, J. Goret, P. Berger, A. Petit, A. De Chevigny, H. Jean-Pierre, B. Nebbad, S. Camiade, R. Meckenstock, V. Lalande, H. Marchandin and F. Barbut.(2015) Prevalence and pathogenicity of binary toxin–positive *Clostridium difficile* strains that do not produce toxins A and B. *New Microbes and New Infections*, Volume 3.

Centers for Disease Control and Prevention (CDC). Severe *Clostridium difficile*-associated disease in populations previously at low risk-four states, 2005. MMWR Morb Mortal Wkly Rep 2005;54:1201–5.

Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol*, 31(5): 431 – 455.

Daniel E. Voth and Jimmy D. Ballard. (2005) *Clostridium difficile* Toxins: Mechanism of Action and Role in Disease. *Clin Microbiol Rev*, 18(2): 247–263.

Daniel R. Knight, Briony Elliott, Barbara J. Chang, Timothy T. Perkins, Thomas V. Rileya. (2015) Diversity and Evolution in the Genome of *Clostridium difficile*. Vol 28(3) Clinical Microbiology Review.

Daniel A. Solomon and Danny A. Milner. (2014) ID Learning Unit: Understanding and Interpreting Testing for *Clostridium difficile*. *Open Forum Infect Dis*, 1(1): ofu007.

Daniel Ww. Biostatistic: A foundation for Analysis in the health Sciences. 7th Edition. 1999. New York, USA. John Wiley and Sons.

Davies AH, Roberts AK, Shone CC, Acharya KR. (2011) Super toxins from a super bug: structure and function of *Clostridium difficile* toxins. *Biochem J* , 436: 517-26.

David A. Enoch and Sani H. Aliyu. (2012) Is *Clostridium difficile* infection still a problem for hospitals? *Canadian Medical Association Journal*, 184 (1) 17-18; DOI: https://doi.org/10.1503/cmaj.111449 184(1): 17–18.

Deirdre A Collins, Peter M Hawkey and Thomas V Riley. (2013) Epidemiology of *Clostridium difficile* infection in Asia. *Antimicrobial Resistance and Infection Control*, 2:21.

Dena Lyras, Jennifer R. O'Connor, Pauline M. Howarth, Susan P. Sambol, Glen P. Carter, Tongted Phumoonna, Rachael Poon, Vicki Adams, Gayatri Vedantam, Stuart Johnson, Dale N. Gerding, and Julian I. Rood. Toxin B is essential for virulence of *Clostridium difficile*.PMC 2009. 458(7242):1176-1179.

Deshpande A, Pasupuleti V, Thota P, Pant C, Rolston DD, Sferra TJ, Hernandez AV, Donskey CJ. Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. *J Antimicrob Chemother.* 2013;68(9):1951-61. doi: 10.1093/jac/dkt129. Epub 2013 Apr 25.

Deshpande A, Pasupuleti V, Thota V, Pant C, David D. K. Rolston, Sferra TJ, Adrian V. Hernandez and Donskey CJ. (2013) Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. *Journal of Antimicrobial Chemotherapy* , 68: 1951–1961.

Dharmarajan T, Sipalay M, Shyamsundar R, Norkus E, Pitchumoni C. (2000) Co-morbidity, not age predicts adverse outcome in *Clostridium difficile* colitis. *World J Gastroenterol*, 6, pp. 198-201.

Dietrich CG, Kottmann T, Alavi M. (2014) Commercially available probiotic drinks containing Lactobacillus casei DN-114001 reduce antibiotic-associated diarrhea. *World J Gastroenterol* , 20: 15837-15844.

Dubberke ER, Reske KA, Yan Y, Olsen MA, McDonald LC, Fraser VJ. (2007) *Clostridium difficile*-associated disease in a setting of endemicity: identification of novel risk factors. *Clin Infect Dis* , 45(12):1543-9. doi: 10.1086/523582.

DuPont Herbert L. (2011) The Search for effective treatment of *Clostridium difficile* infection. *N Engl J Med* , 364:473-475. DOI: 10.1056/NEJMe1013236.

Dominguez SR, Dolan SA, West K, Dantes RB, Epson E, Friedman D, Littlehorn CA, Arms LE, Walton K, Servetar E, Frank DN, Kotter CV, Dowell E, Gould CV, Hilden JM, Todd JK. (2014). High colonization rate and prolonged shedding of *Clostridium difficile* in pediatric oncology patients. *Clin Infect Dis* 59:401–403. 10.1093/cid/ciu302. CrossRefMedlineGoogle Scholar.

Doyle M.E. (2013) *Clostridium difficile* as a Risk Associated with Animal Sources. Food Research Institute University of Wisconsin–Madison, Madison WI 53706.

Esteban-Vasallo MD, Naval Pellicer S, Domínguez-Berjón MF, Cantero Caballero M, Asensio Á, Saravia G, Astray-Mochales J. (2016) Age and gender differences in *Clostridium difficile*-related hospitalization trends in Madrid (Spain) over a 12-year period. *Eur J Clin Microbiol Infec D*, 35(6):1037-44. doi: 10.1007/s10096-016-2635-7. Epub 2016 Apr 7.

Eyre DW, Cule ML, Wilson DJ. (2013). Diverse sources of *Clostridium difficile* infection identified on whole-genome sequencing. *N Engl J Med* , 369:1195-120

Eijiro Ozaki, Haru Kato, Hiroyuki Kita, Tadahiro Karasawa, Tsuneo Maegawa, Youko Koino, Kazumasa Matsumoto,Toshihiko Takada, Koji Nomoto, Ryuichiro Tanaka and Shinichi Nakamura. (2004) *Clostridium difficile* colonization in healthy adults: transient colonization and correlation with enterococcal colonization. *Journal of Medical Microbiology*, 53, 167–172.

Elaine Cheong, Tamalee Roberts, Sayaphet Rattanavong, Thomas V Riley,Paul N Newton, David AB Dance. (2017) *Clostridium difficile* infection in the Lao People's Democratic Republic: first isolation and review of the literature. *BMC Infectious Diseases* , 635 DOI.

Elaine E. Hamm, Daniel E. Voth, and Jimmy D. Ballard. (2006) Identification of *Clostridium difficile* toxin B cardiotoxicity using a zebrafish embryo model of intoxication. PNAS. 103 (38) 14176-14181.

Esac-3 HCSG. Report on point prevalence survey of antimicrobial prescription in European hospitals, 2009. Belgium: University of Antwerp; 2009.

Eiseman B, Silen W, Bascom GS (1958). Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery, 44: 854–859.

Eyre DW, Cule ML, Wilson DJ, Griffiths D, Vaughan A, O'Connor L, Ip CLC, Golubchik T, Batty EM, Finney JM, Wyllie DH, Didelot X, Piazza P, Bowden R, Dingle KE, Harding RM, Crook DW, Wilcox MH, Peto TEA, Walker AS. (2013) Diverse sources of *C. difficile* infection identified on whole-genome sequencing.*N Engl J Med* , 369(13):1195-205. doi: 10.1056/NEJMoa1216064.

Fabio Miyajima, Paul Roberts, Andrew Swale, Valerie Price, Maureen Jones, Michael Horan, Nicholas Beeching, Jonathan Brazier, Christopher Parry, Neil Pendleton, Munir Pirmohamed. Characterisation and Carriage Ratio of *Clostridium difficile* Strains Isolated from a Community-Dwelling Elderly Population in the United Kingdom. PloS ONE. 2011 .Vol 6(8).

Faden H.S and Dryja D. (2015) Brief Report: Importance of asymptomatic shedding of *Clostridium difficile* in environmental contamination of a neonatal intensive care unit. *American Journal of Infection Control* 43. 887-8.

Fernanda C Lessa Yi, Mu , Wendy M Bamberg, Zintars G Beltav, Ghinwa K Dumyati, John R. Dunn, D.V.M, Monica M. Farley, Stacy M. Holzbauer, James I. Meek, Erin C. Phipps, Lucy E. Wilson, Lisa G. Winston, Jessica A. Cohen, Brandi M. Limbago, Scott K. Fridkin, Dale N. Gerding, and L. Clifford McDonald. (2015) Burden of *Clostridium difficile* Infection in the United States. *N Engl J Med* ,372: 825–834.

Figueroa I, Johnson S, Sambol SP, Goldstein EJ, Citron DM, Gerding DN. (2012) Relapse versus reinfection: recurrent *Clostridium difficile* infection following treatment with fidaxomicin or vancomycin. *Clin Infect Dis* , 55: S104-S109.

Florian Prechter, Katrin Katzer, Michael Bauer and Andreas Stallmach.(2017) Sleeping with the enemy: *Clostridium difficile* infection in the intensive care unit. Critical Care 21:260 DOI 10.1186/s13054-017-1819-6.

Fluit AC, Wolfhagen MJ, Verdonk GP, Jansze M, Torensma R, Verhoef J. (1991) Nontoxigenic strains of *Clostridium difficile* lack the genes for both toxin A and toxin B. *J Clin Microbiol*, 29(11):2666-7.

Furuya-Kanamori L, Stone JC, Clark J, McKenzie SJ, Yakob L, Paterson DL, Riley TV, Suhail AR, Clement AC. (2014) Comorbidities, exposure to medications, and the risk of community-acquired *Clostridium difficile* infection: a systematic review and meta-analysis. Infect Control Hosp Epidemiol ;36:132e41.

Gabriel. A.L and Beriot-Mathiot. Hospitalization stay and costs attributable to *Clostridium difficile* infection: a criticle review. *Journal of Hospital infection.* 88 (2014) 12-21.

Gayatri Vedantam, Andrew Clark , Michel Chu, Rebecca Mcquade , MIcheal Mallozzi M, Viswanathan V.K. (2012) *Clostridium difficile* infection.Toxin and non-toxin virulence factors and their contributions to disease establishment and host response.*Gut Microbes*.3:2, 121-134.

Gerding DN, Johnson S, Rupnik M, Aktories K. (2014) *Clostridium difficile* binary toxin CDT: mechanism, epidemiology, and potential clinical importance. *Gut Microbes* 5:15–27. doi:10.4161/gmic.26854.

Geric Stare B, Rupnik M. (2010) *Clostridium difficile* toxinotype XI (A−B−) exhibits unique arrangement of PaLoc and its upstream region. *Anaerobe*, 16:393–5.

Ghose C. (2013) *Clostridium difficile* infection in the twenty-first century. *Emerging Microbes and Infections*, e62; doi:10.1038/emi.2013.62 2013 SSCC. All rights reserved 2222-1751/13.

Giulio DiDiodato, Leslie McArthur. (2016) Evaluating the Effectiveness of an Antimicrobial Stewardship Program on Reducing the Incidence Rate of Healthcare Associated *Clostridium difficile* Infection: A Non-Randomized, Stepped Wedge, Single Site, Observational Study. *PLOS ONE | DOI:10.1371/journal.pone.0157671.*

Greta Roncarati, Laura Dallolio, Erica Leoni, Manuela Panico, Angela Zanni and Patrizia Farruggia.(2017) Surveillance of *Clostridium difficile* Infections: Results from a Six-Year Retrospective Study in Nine Hospitals of a North Italian Local Health Authority. *Int. J. Environ. Res. Public Health*, 14, 61.

Gough E, Shaikh H & Manges AR.(2011) Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. *Clin Infec Dis* ;53(10):994–1002.

Guo B, Harstall C, Louie T, Veldhuyzen van Zanten S, Dieleman LA. (2012) Systematic review: faecal transplantation for the treatment of *Clostridium difficile*-associated disease. *Aliment Pharmacol Ther* ; 35(8):865-75. doi: 10.1111/j.1365-2036.2012.05033.x.

Gupta A, Khanna S. (2014) Community-acquired *Clostridium difficile* infection: an increasing public health threat. *Infect Drug Resist* , 7:63-72.

Harbarth S, Samore MH. (2012) *Clostridium*: Transmission *difficile*? *PLoS Med* , 9(2):e1001171. doi: 10.1371/journal.pmed.1001171.

Harminder Singh, Zoann Nugent, B. Nancy Yu, Lisa M. Lix, Laura Targownik, Charles Bernstein.(2017) Research Article: Hospital discharge abstracts have limited accuracy in identifying occurrence of *Clostridium difficile* infections among hospitalized individuals with inflammatory bowel disease: A population-based study.PLoS ONE.Vol 12:1-10.

Hassan SA, Othman N, Mohd Idris F, Abdul Rahman Z, Maning N, Abdul Rahman R, Chan Guan Tiong. (2012) Prevalence of *Clostridium difficile* toxin in diarhoeal stool samples of patients from a tertiary hospital in North Eastern Penisular Malaysia. *Med J Malaysia*. 67(4)402-405.

Hautmann MG, Hipp M, Ko ¨lbl O. (2011) *Clostridium difficile*-associated diarrhea in radiooncology: an underestimated problem for the feasibility of the radiooncological treatment? *Radiat Oncol* ;6:89.

Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, Johnsen B, Shekelle PG. (2012) Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA* ;307 (18):1959–69.

Henrich TJ, Krakower D, Bitton A, Yokoe DS. (2009) Clinical risk factors for severe *Clostridium difficile*-associated disease. Emerg Infect Dis;15(3):415-22. doi: 10.3201/eid1503.080312.

Hensgens MPM, Goorhuis A, Dekkers OM, Kuijper EJ (2012) Time interval of increased risk for *Clostridium difficile* infection after exposure to antibiotics. *J Antimicrob Chemther* 67:742–748.

Hensgens MP, Keessen EC, Squire MM, Riley TV, Koene MG, de Boer E, Lipman LJ, Kuijper EJ (2012) European Society of Clinical Microbiology and Infectious Diseases Study Group for *Clostridium difficile* (ESGCD). Clostridium difficile infection in the community: a zoonotic disease?. 2012 Jul;18(7):635-45. doi: 10.1111/j.1469-0691.2012.03853.x.

Hiroyuki Kubota, Hiroshi Makino, Agata Gawad, Akira Kushiro, Eiji Ishikaw, Takafumi Sakai, Takuya Akiyama, Kazunori Matsuda, Rocio Martin, Jan Knol, Kenji Oishia. (2016) Longitudinal investigation of carriage rates, counts, and genotypes of toxigenic *Clostridium difficile* in early infancy. *Applied and Environmental Microbiology.* Vol 82:19.

Hong Qiu, Cassan R, Johnstone D, Han X, Joyee AG, McQuoid M, Masi A, Merluza J, Hrehorak B, Reid R, Kennedy K, Tighe B, Rak C, Leonhardt M, Dupas B, Saward L, Berry JD, Nykiforuk CL. (2016) Novel *Clostridium difficile* Anti Toxin (tdcA and tdcB) Humanized Monoclonal Antibodies Demonstrate in Vitro Neutralization across a Broad spectrum of clinical strains and In Vivo Potency in a Hamster Spore Challenge Model. *PLUS ONE*, DoI : 10.1371/journal.pone.0157970.

Högenauer C, Langner C, Beubler E, Lippe IT, Schicho R, Gorkiewicz G, Krause R, Gerstgrasser N, Krejs GJ, Hinterleitner TA. (2006) Klebsiella oxytoca as a causative organism of antibiotic- associated hemorrhagic colitis. *N Engl J Med* , 355: 2418-2426 [PMID: 17151365].

Holloway KA. (2011) Promoting the rational use of antibiotics. Regional Health Forum. WHO South East Asia Region, 15(1):122–130.

Horan TC, Andrus M, Dudeck MA. (2008) CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* , 36(5): 309-32.

Hounnou G, Destrieux C, Desmé J, Bertrand P, Velut S.(2002) Anatomical study of the length of the human intestine. *Surg Radio Anat*, 24(5):290-4. Epub 2002 Oct 10.

Hsu L.Y, Tan T.Y, Koh T.H, Kwa A.L, Krishnan P, Tee N.W, Jureen R. (2011) Decline in *Clostridium difficile*-associated disease rates in Singapore public hospitals, 2006 to 2008. *BMC Research* Notes, 4:77.

Huang H, Fang H, Weintraub A, Nord CE. (2009) Distinct ribotypes and rates of antimicrobial drug resistance in *Clostridium difficile* from Shanghai and Stockholm. *Clin Microbiol Infect*, 15(12):1170–1173.

Huang H, Wu S, Wang M, Zhang Y, Fang H, Palmgren AC, Weintraub A, Nord CE . (2008) Molecular and clinical characteristics of *Clostridium difficile* infection in a University Hospital in Shanghai. China. *Clin Infect Dis*, 47(12):1606–1608.

Huang H, Wu S, Wang M, Zhang Y, Fang H, Palmgren AC, Weintraub A, Nord C. (2009) *Clostridium difficile* infections in a Shanghai hospital: antimicrobial resistance, toxin profiles and ribotypes. *Int J Antimicrob Agents*, 33(4):339–342.

International Foundation for Functional Gastrointestinal Disorders (2010). "*Clostridium difficile* (C. Difficile)". (2009). http://www.iffgd.org/site/gi-disorders/other/cdifficile.

Jank T, Aktories K. (2008) Structure and mode of action of clostridial glucosylating toxins: the ABCD model. *Trends Microbiol*, 16(5):222-9.

Janezic S, Zidaric V, Pardon B, Indra A, Kokotovic B, Blanco J.L, Diaz C.R, Poxton I.R, Peretten V, Drigo I, Jiraskova A, Ocepek M, Weeese J.S, Songer J.G, Wilcox M.H and Rupnic M. (2014) Research Article: International *Clostridium difficile* animal strain collection and large diversity of animal associated strain. *BMC Microbiology*, 14:173.

Jennifer R. O'Connor, Stuart Johnson, Dale N. Gerding. (2009) *Clostridium difficile* Infection Caused by the Epidemic BI/NAP1/027 Strain. Gastroenterology. Vol 136 (6), Pages 1913–1924.

Jessica S.H Martin, Tanya M.Monaghan and Mark H.Wilcox. (2016) *Clostridium difficile* infection: epidemiology, diagnosis and understanding transmission. Nature reviews. *Gastroenterology and Hepatology*.

Jangi, S. Lamont, J.T. (2010) Asymptomatic colonization by *Clostridium difficile* in infants: implications for disease in later life. *J Pediatr Gastroenterol Nutr*, 51, 2–7.

Jing-Wei Cheng, Meng Xiao, Timothy Kudinha, Fanrong Kong, Zhi-Peng Xu, Lin-Ying Sun, Li Zhang, Xin Fan, Xiu-Li Xie, and Ying-Chun Xu. (2016) Molecular Epidemiology and Antimicrobial Susceptibility of *Clostridium difficile* Isolates from a University Teaching Hospital in China. *Front Microbiol* , 7: 1621.

Johnson S, Adelmann A, Clabots CR, et al. Recurrences of *Clostridium difficile* diarrhea not caused by the original infecting organism. *J Infect Dis* 1989;159:340–343.

Johannis Andreas Karas, Simon Bradshaw, Wabbas Mahmud, and David A. Enoch. Mortality in hospitalized older adults associated with *Clostridium difficile* infection at a district hospital. *Infect Dis Rep.* 2010. 2(1): e8.

Jonathan Swindells, Nigel Brenwald, Nathan Reading and Beryl Oppenheim. Evaluation of Diagnostic Tests for *Clostridium difficile* Infection. *Journal of Clinical Microbiology* 2010.Vol 48 (2 606-608.

Joyanna M Wendt, Jessica A .Cohen, Yi Mu, Ghinwa K. Dumyati, John R.Dunn, Stacy M. Holzbauer, Lisa G. Winston, Helen L. Johnson, James I. Meek, Monica M. Farley, Lucy E. Wilson, Erin C. Phipps, Zintars G.Beldavs, Dale N. Gerding, L. Clifford McDonald, Carolyn V. Gould, Fernanda C. Lessa. *Clostridium difficile* infection Among Children Across Diverse US Geographic Locations. *American Academy of Pediatrics.* (2014), VoL 133 (4).

Justin S, Antony B, Shenoy KV, Boloor R. Prevalence of *Clostridium difficile* among paediatric patients in a tertiary care hospital, Coastal Karnataka, South India. *J Clin Diagn Res* 2015, 9(2):DC04-7.

Kamboj M, Khosa P, Kaltsas A, Babady NE, Son C, Sepkowitz KA. Relapse versus reinfection: surveillance of *Clostridium difficile* infection. *Clin Infect Dis* 2011 :1003-1004.

Kato H, Kita H, Karasawa T, Maegawa T, Koino Y, Takakuwa H. Colonisation and transmission of *Clostridium difficile* in healthy individuals examined by PCR ribotyping and pulsed-field gel electropho- resis. *J Med Microbiol.* 2001; 50: 720–727. PMID: 11478676.

Karanika Stylani, Paudel S, Zervou FN, Grigoras C, Zacharioudakis IM, Mylonakis E. Prevalence and clinical outcomes of *Clostridium difficile* infection in the intensive care unit: a systematic review and meta-analysis. *Open Forum Infect Dis.* 2016; 3:ofv186–10.

Kazuhito Yuhashi (2016). Diagnosing *Clostridium difficile* associated diarrhoea using enzyme immunoessay; the clinical significance of toxin negativity in glutamate dehydrogenase-positive patients. Dove Press Journal: *Infection and Drug Resistance. Infect Drug Resist.* 9: 93–99.

Kelly Ciaran P and LaMont J Thomas. *Clostridium difficile* - More difficult than ever. *N Engl J Med* 2008; 359:1932-1940.

Khanna S, Pardi DS, Aronson SL, Kammer PP, Orenstein R, St Sauver JL, Harmsen WS, Zinsmeister AR. (2012) The epidemiology of community-acquired *Clostridium difficile* infection: a population- based study. *Am J Gastroenterol*, 107: 89-95 [PMID: 22108454 DOI: 10.1038/ajg.2011.398].

Khanafer N, Oltra L, Hulin M, Dauwalder O, Vandenesch F, Vanhems P. (2016) *Clostridium difficile* infection in French University Hospital. *Medicine* (Baltimore) ; 95(23): e3874.

Khan F.Y and Elzouki A.N. Clostridium difficile Infection: a review of the literature. *Asian Pasific Journal of Tropical Medicine* 2014;7 (Suppl 1):S6-S13. Science Direct.

Kim J, Shaklee JF, Smathers S, et al. Risk factors and outcomes associated with severe *Clostridium difficile* infection in children. *Pediatr Infect Dis J.* 2012;31(2):134–138. doi: 10.1097/INF.0b013e3182352e2c.

Kim YS, Han DS, Kim YH, Kim WH, Kim JS, Kim HS, Park YS, Song HJ, Shin SJ, Yang SK. (2013): Incidence and clinical features of *Clostridium difficile* infection in Korea: a nationwide study. *Epidemiol Infect*, 141(1):189–194.

Kim J, Kang JO, Kim H, Seo MR, Choi TY, Pai H, Kuijper EJ, Sanders I, Fawley W: Epidemiology of *Clostridium difficile* infections in a tertiary-care hospital in Korea. *Clin Microbiol Infect* 2013, 19(6):521–527.

Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. 2008. Epidemiological features of *Clostridium difficile*-associated disease among inpatients at children's hospitals in the United States, 2001-2006. *Pediatrics* 122:1266–1270.

Kikkawa H, Hitomi S, Watanabe M. (2007) Prevalence of toxin A-nonproducing/toxin-B-producing *Clostridium difficile* in the Tsukuba-Tsuchiura district, Japan. Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases 2007. 13:35–38.

Knetsch C.W, Lawley T.D, Hensgen M.P, Corver J, Wilcox M.W, Kujiper E.J. (2013) Research Article: Current application and future perspectives of molecular typing methods to study *Clostridium difficile* infections.

Knight D.R, Elliott B, Chang B.J, Perkins T.T, Riley T.V. (2015) Diversity and Evolution in the Genome of *Clostridium difficile*. *Clinical*. Vol 28(3).pg

Kuntz JL, Chrischilles EA, Pendergast JF, Herwaldt LA, Polgreen PM. (2011) Incidence of and risk factors for community associated *Clostridium difficile* infection: A nested case-control study. *BMC Infectious Diseases*, 11(194).

Koh TH, Tan AL, Tan ML, Wang G and Song KP. Epidemiology of *Clostridium difficile* infection in a large teaching hospital in Singapore. *Pathology* (2007) 39(4), pp. 438–442.

Koenigsknecht MJ, Theriot CM, Bergin IL, Schumacher CA, Schloss PD, Young VB. (2015) Dynamics and establishment of *Clostridium difficile* infection in the murine gastrointestinal tract. *Infect Immune.* 83(3):934-41. doi: 10.1128/IAI.02768-14.

Khennavong M, Davone V, Vongsouvath M, Phetsouvanh R, Silisouk J, Rattana O, Mayxay M, Castonguay-Vanier J, Moore CE, Strobel M (2011). Urine antibiotic activity in patients presenting to hospitals in Laos: implications for worsening antibiotic resistance. *Am J Trop Med Hyg* ;85(2):295–302.

Kuehne SA, Cartman ST, Heap JT, Kelly ML, Cockayne A, Minton NP. (2010) The role of toxin A and toxin B in *Clostridium difficile* infection. 2014. *Nature* 467:711–713.

Kuehne SA, Collery MM, Kelly ML, Cartman ST, Cockayne A, Minton NP. (2014) Importance of toxin A, toxin B, and CDT in virulence of an epidemic *Clostridium difficile* strain. *J Infect Dis* 209:83–86. doi:10.1093/infdis/jit426.

Krutova M, Matejkova J, Nyc OC. Difficile ribotype 027 or 176? *Folia Microbiol* (Praha). 2014; 59: 523-6.

Kyne L, Hamel MB, Polavaram R, Kelly CP. (2002) Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile. Clin Infect Dis* ;34:346–353.

Kyne L, Farrell R, Kelly CP. (2011) *Clostridium difficile. Gastroenterol Clin North Am*;30(3):753–777.22.

Kyne, L., M. Warny, A. Qamar, and C. P. Kelly. 2001. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. *Lancet* 357:189-193.

Kyne L, Merry C, O'Connell B, Kelly A, Keane, O'Neill D. (1999) Factors associated with prolonged symptoms and severe disease due to *Clostridium difficile.* Age Ageing, 28, pp. 107-113.

Kyne L, Warny M, Qamar A, Kelly CP. (2001) Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. Lancet, 357: 189–93.

Latisha Heinlen and Jimmy D. Ballard. *Clostridium difficile* infection. *Am J Med Sci.* 2010, 340(3): 247–252.

Larcombe S, Hutton ML, Lyras D. (2006) Involvement of Bacteria Other Than *Clostridium difficile* in Antibiotic-Associated Diarrhoea. *Trends Microbiol* , 24: 463-476.

Lavanya Segar, Joshy M Easow, Sreenivasan Srirangaraj, Mohammad Hanifah, Noyal M Joseph, KS Seetha. (2017) Prevalence of *Clostridium difficile* infection among the patients attending a tertiary care teaching care hospital.Indian *Journal of Pathology and Microbiology.* Vol 60(2). Pg 221-225.

Lee JH, Lee Y, Lee K, Riley TV, Kim H. (2014) The changes of PCR ribotype and antimicrobial resistance of *Clostridium difficile* in a tertiary care hospital in Korea over 10 years. *J Med Microbiol* ; 63(Pt 6): 819–23.

Leffler DA, Lamont JT. (2015)*Clostridium difficile* infection. *N Engl J Med* ;372(16):1539-48. doi: 10.1056/NEJMra1403772.

Leibowitz J, Soma VL, Rosen L, Ginocchio CC, Rubin LG. (2015) Similar proportions of stool specimens from hospitalized children with and without diarrhea test positive for *Clostridium difficile. Pediatr Infect Dis J* 34: 261–266.

Linda S and Alison Twy. (2003) The difference between incidence and prevalence. *Paediatric Nursing.* Vol 15(7).

Lim PL, Barkham TM, Ling LM, Dimatatac F, Alfred T, Ang B. (2008) Increasing incidence of *Clostrodium difficile*-associated disease, Singapore. *Emerg Infect Dis*, 14:1487-9.

Liubakka A, MD Byron P. Vaughn BP. *Clostridium difficile* Infection and Fecal Microbiota Transplant. AACN Advanced Critical Care VoL 27(3), pp. 324-337.

Lteif L. (2017) Updates on *Clostridium difficile* Infection: Advances in Laboratory Testing to Aid Diagnosis and Treatment. *Hawai Journal of Medicine and Public Health.* (2017). Vol 76(2).

Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frenette C, Kelly M, Vibien A, Brassard P, Fenn S, Dewar K, Hudson TJ, Horn R, René P, Monczak Y, Dascal A. (2015) A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med.* 353(23):2442-9.

Lorraine Kyne, Michel Warny, Amir Qamar, Kelly CP. (2000) Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A.*N Engl J Med.* 342(6):390-7.

Lungulescu OA, Cao W, Gatskevich E, Tlhabano L, Stratidis JG. (2011) CSI: a severity index for *Clostridium difficile* infection at the time of admission. *J Hosp Infect*, 79, pp. 151-154.

Lyerly DM, Saum KE, MacDonald DK, Wilkins TD. Effects of *Clostridium difficile* toxins given intragastrically to animals. *Infect Immunol* 1985; 47: 349–52.

Lynne Vernice McFarland, Metehan Ozen, Ener Cagri Dinleyici, Shan Goh. (2016) Comparison of pediatric and adult antibiotic-associated diarrhoe and *Clostridium difficile* infections. *World J Gastroenterol* , 22(11): 3078-3104.

Lyras LD, O'Connor JR, Howarth PM, Sambol SP, Carter GP, Phumoonna T, Poon R, Adams V, Vedantam G, Johnson S, Gerding DN, Rood JI. (2009) Toxin B is essential for virulence of *Clostridium difficile*. *Nature*, 458:1176–1179. [PubMed: 19252482]

McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Kelly C. (2018) Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clinical Infectious Diseases*, Vol 66(7), Pages e1–e48.

Martin J.S.H, Monaghan T.M and Wilcox M.H.(2016) *Clostridium difficile* infection: epidemiology, diagnosis and understanding transmission. *Gastroenterology and Hepatology*.

Martinez-Melendez A, Camacho-Ortiz A, Morfin-Otero Rayo, Maldonado-Garza H.J, Villareal-Trevino L and Garza-Gonzalez E. (2017) Current knowledge on the laboratory diagnosis of *Clostridium difficile* infection. *World Journal of Gastroenterology*. 23(9): 1552-1567.

Martinson JN, Broadaway S, Lohman E, Johnson C, Alam MJ, Khaleduzzaman M, Garey KW, Schlackman J, Young VB, Santhosh K, Rao K, Lyons RH Jr, Walk ST. (2015) Evaluation of portability and cost of a fluorescent PCR ribotyping protocol for *Clostridium difficile* epidemiology. *J Clin Microbiol.* 53(4):1192-1197.

Martin J.S.H, Monaghan T.M and Wilcox M.H. (2016) Review*: Clostridium difficile* infection: epidemiology, diagnosis and understanding transmission. *Nat Rev Gastroenterol Hepatol.* 13(4):206-16. doi: 10.1038/nrgastro.2016.25.

Martijn P Bauer, Daan W Notermans, Birgit HB van Benthem, Jon S Brazier, Mark H Wilcox, Maja Rupnik, Dominique L Monnet, Jaap Tvan Dissel, Ed J Kuijper. (2011) *Clostridium difficile* infection in Europe: a hospital-based survey. Vol 377(9759), Pg 63-73.

Marston HD, Dixon DM, Knisely JM, Palmore TN, Fauci AS (2016) Antimicrobial resistance. *JAMA* 316:1193–1204. https://doi.org/10.1001/jama.2016.11764 PMID: 27654605.

Mary Y. Hu, Kianoosh Katchar, Lorraine Kyne, Seema Maroo, Sanjeev Tummala, Valley Dreisbach, Hua Xu, Daniel A. Leffler, Ciarán P. Kelly. (2009) Prospective Derivation and Validation of a Clinical Prediction Rule for Recurrent *Clostridium difficile* Infection. *Gastroenterology*. Vol 136(4), Pg 1206–1214.

Matsuki S, Ozaki E, Shozu, M.; Inoue, M.; Shimizu, S.; Yamaguchi, N.; Karasawa, T.; Yamagishi, T.; Nakamura, S. (2005) Colonization by *Clostridium difficile* of neonates in a hospital, and infants and children in three day-care facilities of Kanazawa, Jpn. *Int. Microbiol*, 8, 43–48.

Mavros MN, Alexiou VG, Vardakas KZ, Tsokali K, Sardi TA, Falagas ME. (2012) Underestimation of *Clostridium difficile* infection among clinicians: an international survey. *Eur J Clin Microbiol Infect Dis*, 31(9):2439-2444.

McFarland LV. (2008) Antibiotic-associated diarrhea: epidemiology, trends and treatment. *Future Microbiol.* 3(5):563–78.

Miller M, Gravel D, Mulvey M, Taylor G, Boyd D, Simor A, am M, McGeer A, Hutchinson J, Moore D, Kelly S.(2010) Healthcare- associated *Clostridium difficile* infection in Canada: patient age and infecting strain type are highly predictive of severe outcome and mortality. *Clin Infect*, 50:194–201.

M Jahangir Alam, A Anu, S T Walk, K W Garey (2014) Investigation of potentially pathogenic *Clostridium difficile* contamination in household environs. *Anaerobe* 27: 31-33.

Moon H.W, Kim H.N, Kim J.Y, Hur M, Kim H, Yun YM.(2016) Performance of the artus *C. difficile* QS-RGQ Kit for the detection of toxigenic. *Clinical Biochemistry*. Science Direct.

Moono P, Lim S.C, Riley T.V.(2017) High prevalence of toxigenic *Clostridium difficile* in public space lawn in Western Australia. Scientific Reports.

Monnier A.L, Zahar J.R and Barbut F. General View: Update on *Clostridium difficile* infections. *Medecine et maladies infectieuses* 44(2015) 354-365.

Monique M Elseviers, Yoleen Van Camp, Sander Nayaert, Duré Khyra, Lieven Annemans, Ann Tanghe, Vermeersch S.(2015) Prevalence and management of antibiotic associated diarrhea in general hospitals. *BMC Infect Dis*, 15: 129 [PMID: 25888351 DOI: 10.1186/s12879-015-08690].

Mori N, Aoki Y.(2015) Clinical characteristics and risk factors for community-acquired *Clostridium difficile* infection: A retrospective, case-control study in a tertiary care hospital in Japan. *J Infect Chemother*, 21(12):864-7. doi: 10.1016/j.jiac.2015.09.004. Epub 2015 Oct 23.

Naaber P, Lehto E, Salminen S, Mikelsaar M. (1999) Inhibition of adhesion of *Clostridium difficile* to Caco-2 cells. FEMS *Immunol Med Microbiol.* 14:205–209.

Nagham Khanafer , Frederic B, Catherine Eckert, Michel Perraud, Clarisse Demont and Christine Luxenburger and Phillipe Vanhems.(2016) Factors predictive of severe *Clostridium difficile* infection depend on the definition used. Anaerobe. Vol 37, Pgs 43-48.

Ngamskulrungroj P, Sanmee S, Pusathit P, Piewngam P, Elliott B, Riley TV, Kiratisin P. Research Article. (2015) Molecular Epidemiology of *Clostridium difficile* Infection in a Large Teaching Hospital in Thailand. PLOS ONE | DOI:10.1371/journal.pone.0127026.

Nienke Z. Borren, Shadi Ghadermarzi, Susan Hutfless, Ashwin N. Ananthakrishnan. (2017) Research Article: The emergence of *Clostridium difficile* infection in Asia: A systematic review and meta-analysis of incidence and impact. PLoS ONE 12(5): e0176797.

Nobuaki Mori and Yasuko Aoki. (2015) Clinical characteristic and risk factors for community acquired *Clostridium difficile* infection: A retrospective, case control study in a tertiary care hospital in Japan. *Journal of Infection and Chemotherapy.*21, 864-867.

Nur Nashyiroh, Zulina Mazlan, Shamsul Bahari Shamsuddin, Mohammad Zahirul Hoque, Khurshida Begum, M Jahangir Alam (2017) First Detection and Characterization of Clostridium difficile Among Hospitalized Children in Sabah, Malaysia In: 10th Malaysian Indonesian Brunei Medical conference, Kuala Lumpur.

Nur Nashyiroh, Ahneez Abdul Hameed, Shamsul Bahari Shamsuddin, M Zahirul Hoque, Khurshida Begum, M Jahangir Alam (2017) Prevalence of Clostridium difficile infection in a tertiary care hospital in Sabah, Malaysia. In: 49th Conference of the Asia-Pacific Academic Consortium for Public Health (APACPH), South Korea.

Nylund CM, Goudie A, Garza JM, Fairbrother G, Cohen MB. (2011) *Clostridium difficile* infection in hospitalized children in the United States. *Arch Pediatr Adolesc Med,* 165(5):451.

O'Connor JR1, Johnson S, Gerding DN. (2009) *Clostridium difficile* infection caused by the epidemic BI/NAP1/027 strain. *Gastroenterology,* 136(6):1913-24.

Oleastro M, Coelho M, Gião M, Coutinho S, Mota S, Santos A, Rodrigues J, Faria D. Outbreak of *Clostridium difficile* PCR ribotype 027–the recent experience of a regional hospital. BMC Infect Dis. 2014; 14: 209.

Patrizia Spigaglia. (2016) Recent advances in the understanding of antibiotic resistance in *Clostridium difficile* infection. *Therapeutic Advances in Infectious Disease*. 3(1) 2342.

Pepin J, Saheb N, Coulombe MA, Coulombe MA, Alary ME, Corriveau MP, Authier S, Leblanc M, Rivard G, Bettez M, Primeau V, Nguyen M, Jacob CE, Lanthier L.(2005) Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhoea: a cohort study during an epidemic in Quebec. *Clin Infect Dis*, 41:1254-60.

Peled N, Pitlik S, Samra Z, Kazakov A, Bloch Y, Bishara J. (2007) Predicting *Clostridium difficile* toxin in hospitalized patients with antibiotic-associated diarrhea. *Infect Control Hosp Epidemiol*, 28: 377-381.

Persson S, Torpdahl M, Olsen KE. (2008) New multiplex PCR method for the detection of *Clostridium difficile* toxin A (tcdA) and toxin B (tcdB) and the binary toxin (cdtA/cdtB) genes applied to a Danish strain collection. *Clin Microbiol Infect*, 14(11):1057-64. doi: 10.1111/j.1469-0691.2008.02092.x. Erratum in: Clin Microbiol Infect 2009, 15(3):296. PubMed PMID: 19040478.

Peterson, L. R., R. U. Manson, S. M. Paule, D. M. Hacek, A. Robicsek, R. B. Thomson, Jr., and K. L. Kaul. (2007) Detection of toxigenic *Clostridium difficile* in stool samples by real-time polymerase chain reaction for the diagnosis of *C. difficile*-associated diarrhea. *Clin Infect Dis*. 45:1152-1160.

Pituch H, Obuch-Woszczatyński P, Wultańska D, van Belkum A, Meisel-Mikołajczyk F, Łuczak M.(2007) Laboratory diagnosis of antibiotic-associated diarrhea: a Polish pilot study into the clinical relevance of *Clostridium difficile* and *Clostridium perfringens* toxins. *Diagn Microbiol Infect Dis*, 58: 71-75.

Polage CR, Solnick JV, Cohen SH. Nosocomial diarrhea: evaluation and treatment of causes other than *Clostridium difficile*.Clin Infect Dis. 2012; 55(7):982-9.

Popchai Ngamskulrungroj, Sittinee Sanmee, Papanin Pusathit, Pipat Piewngam, Briony Elliott, Thomas V. Riley, Pattarachai Kiratisi. (2015) Molecular Epidemiology of *Clostridium difficile* Infection in a Large Teaching Hospital in Thailand. *PLOS ONE*, doi.org/10.1371/journal.pone.0127026

Popiel K.Y, Gheorghe R, Eastmond J, Miller M.A. (2015) Usefulness of Adjunctive Fecal Calprotectin and Serum Procalcitonin in Individuals Positive for *Clostridium difficile* Toxin Gene by PCR Assay. *Journal of Clinical Microbiology*, Vol 53(11).

Putsathit P, Kiratisin P, Ngamwongsatit P, Riley TV. (2015) *Clostridium difficile* infection in Thailand. *Int J Antimicrob Agents*, 45(1):1-7.

Poutanen SM1, Simor AE. *Clostridium difficile*-associated diarrhea in adults. (2004) *CMAJ*, 171(1):51-8.

Poxton IR, McCoubrey J, Blair G. (2001) The pathogenicity of *Clostridium difficile*. *Clin Microbiol Infect*, 7(8); 421-7.

Quinn, C. D., S. E. Sefers, W. Babiker, Y. He, R. Alcabasa, C. W. Stratton, K. C. Carroll, and Y. W. Tang. 2010. C. Diff Quik Chek Complete enzyme immunoassay provides a reliable first-line method for detection of *Clostridium difficile* in stool specimens. J Clin Microbiol. 48:603-605.

Rao K, Walk ST, Micic D, Chenoweth E, Deng L, Galecki AT, Jain R, Trivedi I, Yu M, Santhosh K, Ring C, Young VB, Huffnagle GB, Aronoff DM.(2003) Procalcitonin Levels Associate with Severity of *Clostridium difficile* Infection. *PLOS One*. Vol8(3).

Rao K and Young V.B. (2015) Fecal Microbiota Transplantation for the Management of *Clostridium difficile* Infection. *Infectious Disease Clinical America*. 29(1); 109-122.

Report on the burden of endemic health care-associated infection worldwide. World Health Organization (WHO) 2011.

Riegler M, R Sedivy, C Pothoulakis, G Hamilton, J Zacherl, G Bischof, E Cosentini, W Feil, R Schiessel, J T LaMont. *Clostridium difficile* toxin B is more potent than toxin A in damaging human colonic epithelium in vitro. *J Clin Invest* 1995; 95(5): 2004–2011.

Robinson CJ, Young VB. (2010) Antibiotic administration alters the community structure of the gastrointestinal micobiota. *Gut Microbes*. 1:279–284. [PubMed: 20953272].

Rodriguez C, Fernandez J, Van Broeck J, Taminiau B, Avesani V, Boga JA, Vazquez F, Delmée M, Daube G. (2016) *Clostridium difficile* presence in Spanish and Belgian hospitals. *Microbial Pathogenesis* 100, 141-148.

Rodriguez C, Korsak N,Taminiau B, Avesani V, J. Broeck V, Delmee M, G. Daube a. (2014) Clinical microbiology. *Clostridium difficile* infection in elderly nursing home residents. *Anaerobe* 30:184e187.

Rodriguez C, Fernandez J, Broeck J.V, Taminiau B, Avesani V, Boga J.A, Vazquez F, Delmee M, Daube G. (2016) *Clostridium difficile* in Spanish and Belgian hospitals. *Microbial Pathogenesis* 100 : 141-148. Science Direct.

Rohlke F and Stollman Neil. (2012) Fecal Microbiota transplantation in relapsing *Clostridium difficile* infection. *Therapeutic Advances in Gastroenterology*, 5(6) 403-420..

Rousseau C, Poilane I, De Pontual L, Maherault AC, Le Monnier A, Collignon A. (2012) *Clostridium difficile* carriage in healthy infants in the community: a potential reservoir for pathogenic strains. *Clin Infect Dis* 55:1209–1215.

Rolfe RD, Song W. (1995) Immunoglobulin and non-immunoglobulin components of human milk inhibit *Clostridium difficile* toxin A-receptor binding. *J Med Microbiol* 42:10–19.

Rupnik M, Wilcox MH, Gerding DN. (2009) *Clostridium difficile* infection: new developments in epidemiology and pathogenesis. *Nat Rev Microbiol*, 7:526–536.

Rupnik M.(2008) Heterogeneity of large clostridial toxins: importance of *Clostridium difficile* toxinotypes. *FEMS Microbiol Rev*, 32:541–55.

Rupnik M and Janezic S. (2016) Mini review: An update on *Clostridium difficile* Toxinotyping. *Journal of Clinical Microbiology*. Vol: 64:1.

Saif N.A and Brazier J.S. (1996) Bacterial Ecology: The distribution of *Clostridium difficile* in the environment of South Wales. *Journal of Medical Microbiology*.Vol 45: 133-137.

Salazar CL, Reyes C, Atehortua S, Sierra P, Correa MM, Paredes-Sabja D, Best E, Fawley WN, Wilcox M, González Á. (2017) Molecular, microbiological and clinical characterization of *Clostridium difficile* isolates from tertiary care hospitals in Colombia. *PLoS One*. 12(9):e0184689.

Samaneh Kouzegaran, Mahmood Ganjifard, and Amir Saber Tanha. (2016) Detection, Ribotyping and Antimicrobial Resistance Properties of Clostridium difficile Strains Isolated From The Cases of Diarrhea. *Mater Sociomed*. 28(5): 324-328.

Sambol SP, Merrigan MM, Tang JK, Johnson S, Gerding DN. (2002) Colonization for the prevention of Clostridium difficile disease in hamsters. *J Infect Dis*, 186:1781-9.

Sanchez TH, Brooks JT, Sullivan PS, Juhasz M, Mintz E, Dworkin MS. (2005) Bacterial diarrhea in persons with HIV infection, United States, 1992-2002. *Clin Infect Dis*, 41:1621–7.

Sandora TJ, Fung M, Flaherty K, Helsing L, Scanlon P, Potter-Bynoe G, Gidengil CA, Lee GM. (2011) Epidemiology and risk factors for *Clostridium difficile* infection in children. *Peadiat Infect Disease J*, 30(7):580-4.

Sarah A Kuehne, Stephen T Cartman, and Nigel P Minton. (2011) Both, toxin A and toxin B, are important in *Clostridium difficile* infection. *Gut Microbes*, 2(4): 252–255.

Schwan C, Stecher B, Tzivelekidis T, van Ham M, Rohde M, Hardt WD, Wehland J, Aktories K. (2009) *Clostridium difficile* toxin CDT induces formation of microtubule-based protrusions and increases adherence of bacteria. *Plos Pathog*. (10):e1000626. doi: 10.1371/journal.ppat.1000626. Epub 2009 Oct 16.

Seekatz A.M, Aas J, Gessert C.E, Rubin T.A, Saman D.M, Bakken J.S, Young V.B. (2014) Recovery of the Gut Microbiome following Fecal Microbiota Transplantation. mbio.asm.org.Vol 5(3).

Shinnichirou Matsuki, Eijiro Ozaki, Makio Shozu, Shinichi Nakamura. Colonización por *Clostridium difficile* en recién nacidos en un hospital y en niños menores de cinco años en tres guarderías de Kanazawa, *Japón International Microbiology*. 8(1):43-48.

Shrestha SK, Sunkesula VCK, Kundrapu S, Tomas ME, Nevandzic MM, Donskey CJ. (2016) Acquisition of *Clostridium difficile* on hands of healthcare personnel caring for patients with resolved *C. difficile* infection. *Infect Control Hosp Epidemiol* ;37:475-477.

Simon Stubbs, Maja Rupnik, Maryse Gibert, Jon Brazier, Brian Duerden, Michel Popoff. (2000) Production of actin-specific ADP-ribosyltransferase (binary toxin) by strains of *Clostridium difficile*. FEMS Microbiology Letters, Vol 186(2), Pages 307–312.

Slimings C, Riley TV. (2014) Antibiotics and hospital-acquired *Clostridium difficile* infection: Update of systematic review and meta-analysis. *J Antimicrob Chemther*.69:881–891.

Sorg JA, Sonenshein AL. (2008) Bile salts and glycine as cogerminants for *Clostridium difficile* spores. *J Bacteriol*,190:2505–2512.

Spigaglia P, Barbanti F, Dionisi AM, Mastrantonio P. (2010) *Clostridium difficile* isolates resistant to fluoroquinolones in Italy: emergence of PCR ribotype 018. *J Clin Microbiol*, 48(8):2892–2896.

Stella Antonara, Amy L. Leber. (2016) Diagnosis of *Clostridium difficile* Infections in Children. *Journal of Clinical Microbiology*. Vol 54:6.

Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. (2011) Cumulative antibiotic exposures over time and the risk of *Clostridium difficile* infection. *Clin Infect Dis*. 1;53(1): 42—8.

Stone N.E, Sidak-Loftis L.C, Sahl J.W, Vazquez A.J, Wiggins K.B, Gillece J.D, Hicks N.D, Schupp J.M, Busch J.D, Keim P, Wagner D.M. (2016) Research Article: More than 50% of *Clostridium difficile* Isolates from Pet Dogs in Flag staff, USA, Carry Toxigenic Genotypes. *PLOS ONE*.

Surawicz CM1, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. (2013) Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*,108(4):478-98; quiz 499. doi: 10.1038/ajg.2013.4. Epub 2013 Feb 26.

Susan M. Poutanen and Andrew E. Simor. (2004) *Clostridium difficile*-associated diarrhea in adults. *CMAJ.* 171(1): 51–58.

Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. (2013) Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol,* 108: 478-498; quiz 499.

Swindells J, Brenwald N, Reading N and Oppenheim B. (2010) Evaluation of Diagnostic Test for *Clostridium difficile* Infection. *Journal of Clinical Microbiology*. Vol 48(2) p 606-608.

Syuhada N, Azimatun NA, Alfizah H, Tzar MN, Ramliza R. (2013) *Clostridium difficile* Infections: Clinico-Epidemiological persprctive. *Med & Health*, 8(2):64-72.

Tan X.Q, Verall A.J, Jureen R, Riley T.V, Collins D.A, Lin R.T, Balm M.N, Chan D, Tambyah P.A. (2014) The emergence of community-onset *Clostridium difficile* infection in a tertiary hospital in Singapore: a cause for concern. *International Journal of Antimicrobial Agents* 43:47-51.

Teresa C. Horan, Mary Andrus, Margaret A. Dudeck.(2008) CDC/NHSN surveillance infections in the acute care setting. Vol 36 (5), Pages 309–332.

Thielman NM, Wilson KH. (2005) Antibiotic-associated colitis. In: Mandell GL, Bennett JE, Doolin R, editors. Principles and practice of infectious diseases. Philadelphia: Churchill Livingstone, p. 1249–63.

Thomas V Riley, Deidre A Collins, Rina Karunakaran, Maria Abdul Kahar, Ariza Adnan, Siti Asma Hassan, Nadiah Hanim Zainul, FR Mohammed Rustam, Z Abd Wahab, Ramliza Ramli, Yeong Yeh Lee, Hamimah Hassan. (2018) High Prevalence of toxigenic and non-toxigenic *Clostridium difficile* in Malaysia. J Clin. Microbiol doi: 10.1128/JCM.00170-18.

Tian T, Zhao J, Yang J, Qiang C, Li Z, Chen J, Xu K, Ciu Q, Li R. (2016) RESEARCH ARTICLE: Molecular Characterization of *Clostridium difficile* Isolates from Human Subjects and the Environment. *PLOS ONE* DOI:10.1371/journal.pone.0151964.

Tickler IA, Goering RV, Whitmore JD, Lynn AN, Persing DH, Tenover FC (2014). Strain types and antimicrobial resistance patterns of *Clostridium difficile* isolates from the United States, 2011 to 2013. *Antimicrob Agents Chemother*;58: 4214–8.

Titov, Lebedekova N, Shabanov A, Tang Y, Stuart H. Cohen AND Silva J. (2000) Isolation and Molecular Characterization of Clostridium difficile Strains from Patients and the Hospital Environment in Belarus. *Journal of Clinical Microbiology*, p. 1200–1202 Vol. 38(3).

Travis J. Kochan, Madeline J. Somers, Alyssa M. Kaiser, Michelle S. Shoshiev, Ada K. Hagan, Jessica L. Hastie, Nicole P. Giordano, Ashley D. Smith, Alyxandria M. Schubert, Paul E. Carlson Jr, Philip C. Hanna . (2017) Intestinal calcium and bile salts facilitate germination of *Clostridium difficile* spores. *PLoS Pathog.* 13(7): e1006443.

Trejo FM, Minnaard J, Perez PF, De Antoni GL. (2006) Inhibition of *Clostridium difficile* growth and adhesion to enterocytes by *Bifidobacterium* supernatants. *Anaerobe* 12:186–193.

Truong C, Schroeder L.F, Gaur R, Anikst V.E, Komo I, Watters C, McCalley E, Kulik C, Pickham D, Lee N.J, Banaei N. (2016) *Clostridium difficile* rates in asymptomatic and symptomatic hospitalized patients using nucleic acid testing. Diagnostic Microbiology and Infectious Disease. Science Direct.

Tse Hsien Koh, Ai Ling Tan, Mee Lee Tan, Grace Wang and Keang Peng Song. (2007) Epidemiology of *Clostridium difficile* infection in a large teaching hospital in Singapore. *Pathology*, 39(4), pp. 438–442.

Tschudin-Sutter S. (2014) Molecular Epidemiology of *Clostridium difficile* for clinical practice. Swiss Med Weekly;144:w13995.

Usacheva E.A, Jin J.P, Peterson L.R. (2016) Host response to *Clostridium difficile* infection diagnostic and detection.J.Glob. *Antimicrob. Resist.* 9,93-101.

Vadde R, Ray A.S, Azad M.R, Oke V, Bhattarai B, Pokharel S, Sivasambu B, Yogarajah M, Bakhit A, Sidhu S, Ghosh M, Schmidt M.F. (2014) Interfaith Medical Center, Kew Gardens, NY. Can Procalcitonin Level predict the development of *Clostridium difficile* infection. *Chest,* 146.

Vaishnavi C. (2015) Fidaxomicin the new drug for *Clostridium difficile* infection. *Indian J Med Microbiol*, 141(4):398–407.

Vaishnavi C, Singh M. (2012) Preliminary investigation of environmental prevalence of *Clostridium difficile* affecting inpatients in a north Indian hospital. *Indian J Med Microbiol,* 30(1):89–92.

Vaishnavi C. (2010) Clinical spectrum & pathogenesis of *Clostridium difficile* associated diseases. *Indian Journal of Medical res,* 131:487-99.

Vaishnavi C, Kochhnar R, Bhasin DK, Thapa BR, Singh K.(1999) Detection of Clostridium difficile toxin by an indigenously developed latex agglutination assay. *Trop Gastroenterol*, 20:33-5.

Vaishanavi C, Bhasin K, Kochhnar R, Singh K. (2000) *Clostridium difficile* toxin and faecal lactoferrin assays in adult patients. *Microbes Infect*; 2:1827-30.

Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. (2013) Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med,368 (5):407-15. doi: 10.1056/NEJMoa1205037.

Vardakas KZ, Polyzos KA, Patouni K, Rafailidis PI, Samonis G, Falagas ME. (2012) Treatment failure and recurrence of Clostridium difficile infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. *Int J Antimicrob Agents*, 40: 1-8.

Viscidi R, Willey S, Bartlett JG. (1981) Isolation rates and toxigenic potential of Clostridium difficile isolates from various patient populations. *Gastroenterology* 81:5–9.

Vendetti N, Zaoutis T, Coffin SE, Sammons JS. (2015) Risk factors for in-hospital mortality among a cohort of children with *Clostridium difficile* infection. *Infect Control Hosp Epidemiol* 36:1183–1189.

Vhairi Wilson Liz Cheek Giovanni Satta Karen Walker Bone Marc Cubbon Diane Citron Dale N. Gerding Martin J. Llewelyn. (2010) Predictors of Death after Clostridium difficile Infection: A Report on 128 Strain-Typed Cases from a Teaching Hospital in the United Kingdom. *Clinical Infectious Diseases*, Vol 50 (12), Pg e77–e81

Viswanathan VK1, Mallozzi MJ, Vedantam G. Clostridium difficile infection: An overview of the disease and its pathogenesis, epidemiology and interventions. Gut Microbes. 2010 Jul;1(4):234-242. Epub 2010 Jun 16.

Vohra P, Poxton IR. Efficacy of decontamination ad disinfectats against Clostridium difficile. J.Med.Microbiaol.2011;60:1218-24.

Walk ST, Micic D, Jain R, Lo ES, Trivedi I, Liu EW. (2012) *Clostridium difficile* ribotype does not predict severe infection. *Clin Infect Dis*, 55:1661e8.

Wanahita A, Goldsmith EA, Musher DM. (2002) Conditions associated with leukocytosis in a tertiary care hospital, with particular attention to the role of infection caused by *Clostridium difficile*. *Clin Infect Dis*;34:1585–1592.

Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, Frost E, McDonald LC. (2005) Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. Lancet, 366(9491):1079-84.

Warren C.A., Labio E., Destura R., Sevilleja J.E., Jamias J.D., Daez M.L. *Clostridium difficile* and Entamoeba histolytica infections in patients with colitis in the Philippines. *Trans R Soc Trop Med Hyg.* 2012;106:424–428.

William J. Bradshaw, April K. Roberts, Clifford C. Shone and K. Ravi Acharya. (2018) The structure of the S-layer of *Clostridium difficile*. *J Cell Commun Signal.* 12(1): 319–331. Published online 2017 Nov 23. doi: 10.1007/s12079-017-0429-z.

Wong KK, Lee R, Watkins RR, Haller N (2016) Prolonged *Clostridium difficile* Infection May Be Associated With Vitamin D Deficiency. *JPEN J Parenter Enteral Nutr* 40: 682–687. doi: 10.1177/0148607114568121 [PubMed]

Wongwanich S., Rugdeekha S., Pongpech P., Dhiraputra C. Detection of *Clostridium difficile* toxin A and B genes from stool samples of Thai diarrheal patients by polymerase chain reaction technique. *J Med Assoc Thai.* 2003;86:970–975.

Wongwanich S, Ramsiri S, Kusum M, Warachit P (2000) *Clostridium difficile* infections in HIV-positive patients. Southeast Asian *J Trop Med Public Health,* 31(3):537–539.

World Health Organization. WHO definition of diarrhea. Accessed on November 13, 2015. Available from: URL: http:// www.who.int/topics/diarrhoea/en/.

World Gastroenterology Organization Global Guidelines. Acute diarrhea in adults and children: a global perspective, 2012: p. 3.

Wu Y.C, Lee J.J, Tsai B.Y, Liu Y.F, Chen C.M, Tien N, Tsai P.J, Chen T.H. (2016) Potentially hypervirulent *Clostridium difficile* PCR ribotype 078 lineage isolates in pigs and possible implications for human in Taiwan. *International Journal of Medical Microbiology* 306: 115-122.

Yamamoto-Osaki T, Kamiya S, Sawamura S, Kai M, Ozawa A. (1999) Growth inhibition of *Clostridium difficile* by intestinal flora of infant faeces in continuous flow culture culture. *J Med Microbiol* , 40:179-87.

Yoldaz O, Altindiz M, Cufali D, Asik G and Kesli R. (2016) A diagnostic algorithm for the detection of *Clostridium difficile*-associated bacteria. *American Society of Microbiology*, 33:80-6.

Zainul NH, Ma ZF, Besari A, Siti Asma H, Rahman RA, Collins DA, Hamid N, Riley TV and Lee YY. Prevalence of Clostridium difficile infection and colonization in a tertiary hospital and elderly community of North-Eastern Peninsular Malaysia. *Epidemiol. Infect* 145:3012-3019.

Zahar J-R, Schwebel C, Adrie C, Garrouste-Orgeas M, Français A, Vesin A (2012). Outcome of ICU patients with *Clostridium difficile* infection. *Crit Care*;16:R215. doi:10.1186/cc11852.

Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. (2007) A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis*; 45: 302-307 [PMID: 17599306].

Zellweger RM, Carrique-Mas J, Limmathurotsakul D, Day NPJ, Thwaites GE, Baker S, Ashley E, de balogh K, Baird K, Basnyat B, Benigno C, Bodhiatta L, Chandratita N, Cooper B, dance D, Dhorda M, van Doorn R, Dougan G, Hoa NT et al. A current perspective on antimicrobial resistance in Southeast Asia. 2017. *J Antimicrob Chemother* 72:2963-2972.

Zhang S, Palazuelos-Munoz S, M.Balsells E, Nair H, Chit A, H.Kyaw M. Research Article: Cost of hospital management of *Clostridium diffcile* infection in United States - a meta-analysis and modeling study. *BMC Infectious Disease* (2016). 16:447.

Zilberberg MD, Tillotson GS, McDonald C. (2010) *Clostridium difficile* infections among hospitalized children, United States, 1997-2006. *Emerg Infect Dis* 16:604–609.

Zimlichman E, Henderson D, Tamir, MHA; Franz C, Song P, Yamin C.K, Keohane C, Denham C.R, Bates D.W. (2013) HealthCare–AssociatedInfections A Meta-analysis of Costs and Financial Impact on the US Health Care System. *JAMA Intern Med*, 173(22):2039-2046.