THE PREVALENCE OF HIV, HEPATITIS B, HEPATITIS C AND SYPHILIS INFECTIONS AMONG BLOOD DONORS IN HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU AND ITS ASSOCIATED RISK FACTORS

DR. ADIBAH BT DAUD

Dissertation Submitted In Partial Fulfillment Of The Requirements For The Degree Of Masters Of Pathology (Haematology)

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LIST OF ABBREVIATIONS

AABB	American Association of Blood Banks
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Antibody to hepatitis B surface antigen
CUE	Confidential unit exclusion
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HSNZ	Hospital Sultanah Nur Zahirah
IgG	Immunoglobulin G
IVDU	Intravenous drug user
LIA	Line immunoassay
MOH	Ministry of Health
MSM	Men who have sex with men
NAT	Nucleic acid testing
NBC	National Blood Centre

OD	Optical density
RLU	Reactive light unit
RPR	Rapid plasma reagin
SUKUSA	Sistem Pengumpulan Maklumat untuk Pusat Kutipan & Pusat Saringan
TML	Transfusion microbiology laboratory
TP	Treponema pallidum
TPPA	Treponema pallidum particle agglutination assay
TTI	Transfusion transmitted infection
VDRL	Venereal Disease Research Laboratory
WHO	World Health Organization

DEFINITION

First time blood donor	A blood donor who has never donated in the same blood centre.
Repeat blood donor	A blood donor who has donated at least once in the past
Seroconvert blood donor	A blood donor who is confirmed positive for a particular TTI in his/her current donation but was negative in the previous donation.
Seropositive blood donor	A blood donor who is found to be positive serologically, for any of the TTI markers tested
Transfusion transmitted infection (TTI)	An infection that is potentially capable of being transmitted by blood transfusion. In context of this study, the infections are HIV, HBV, HCV, and Syphilis.

ABSTRAK

PREVALENS BAGI JANGKITAN HIV, HEPATITIS B, HEPATITIS C, DAN SIFILIS DI KALANGAN PENDERMA DARAH DI HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU DAN FAKTOR-FAKTOR RISIKO YANG BERKAITAN

Pengenalan: Transfusi darah dan komponen darah merupakan salah satu pendekatan yg diamalkan dalam perubatan moden bagi merawat pesakit, terutamanya pesakit yang mengalami kekurangan atau kehilangan darah yang banyak. Pendekatan ini bukanlah tanpa risiko, di mana antara risiko tersebut ialah jangkitan yang tersebar melalui transfusi. Kajian ini bertujuan untuk mengenalpasti kelaziman jangkitan HIV, hepatitis B (HBV), hepatitis C (HCV) dan sifilis di kalangan penderma darah di HSNZ dan faktor-faktor risiko yang berkaitan. **Kaedah kajian**: Kajian kawalan kes secara retrospektif ini melibatkan kajian semula rekod penderma darah dari tahun 2011 sehingga 2017. Penderma serologi positif dikenalpasti berdasarkan keputusan ujian-ujian serologi. Data para penderma darah diambil dari sistem atas talian E-delphyn. Data bagi penderma yang didapati positif serologi pula diambil dari sistem atas talian SUKUSA dan rekod kaunseling penderma. Bagi mengkaji perhubungan antara ciri-ciri sosiodemografik dan serologi positif, sekumpulan penderma darah dengan keputusan serologi negatif dipilih secara rawak, sebagai kumpulan kawalan. Data dianalisa dengan menggunakan perisian SPSS versi 24. **Keputusan:** Jumlah pendermaan darah adalah sebanyak 94 989 dari tahun 2011 sehingga 2017, dengan majoriti pendermaan adalah daripada Melayu (91.6%), lelaki (66.1%), pelajar (53.4%), penderma ulangan (61.3%), dan kutipan dari unit bergerak (84.7%). Terdapat sejumlah 330 pendermaan serologi

positif dengan prevalens keseluruhan 0.35%. Jangkitan HBV mencatatkan prevalens tertinggi (0.171%) diikuti oleh HCV (0.113%), sifilis (0.04%), dan HIV (0.024%). Terdapat 13 penderma menunjukkan penukaran serologi (0.014%) dengan penukaran paling tinggi didapati dengan jangkitan HIV (5), diikuti oleh HCV (4), HBV (3) dan sifilis (1). Majoriti faktor risiko yang dikenalpasti di kalangan penderma darah serologi positif adalah amalan seks yang tidak selamat (51.7%), diikuti oleh sejarah keluarga (38.3%), penggunaan ubat intravena (8.3%), dan sejarah transfusi darah (1.7%). Faktor-faktor risiko ini menunjukkan perhubungan yang signifikan dengan kesemua jangkitan-jangkitan yang tersebut (nilai $p<0.05$). Analisis menggunakan logistik regresi berbilang menunjukkan kemungkinan untuk serologi positif adalah lebih tinggi dengan signifikan di kalangan lelaki berbanding perempuan, penderma pertama berbanding penderma ulangan, pekerjaan selain daripada kakitangan kerajaan berbanding pelajar dan pendermaan di unit bergerak berbanding pendermaan di pusat pendermaan darah (nilai $p<0.05$). **Kesimpulan:** Prevalens penderma darah serologi positif dan penukaran serologi di HSNZ adalah rendah dengan HBV merupakan jangkitan paling tinggi. Faktor risiko berkaitan yang paling kerap ialah amalan seks tidak selamat. Lelaki, pendermaan pertama, bukan pelajar, dan pendermaan di unit bergerak menunjukkan risiko lebih tinggi yang signifikan bagi serologi positif.

(379 patah perkataan)

ABSTRACT

THE PREVALENCE OF HIV, HEPATITIS B, HEPATITIS C, AND SYPHILIS INFECTIONS AMONG BLOOD DONORS IN HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU AND ITS ASSOCIATED RISK FACTORS.

Introduction: Blood and blood products transfusion are among the measures used in modern medicine to manage patients, especially those who are anaemic or having significant blood loss. This measure is not without risk, with one of the concerned risk is transfusion transmitted infection (TTI). This study was aimed to determine the prevalence of HIV, hepatitis B (HBV), hepatitis C (HCV) and syphilis infections among blood donors in Hospital Sultanah Nur Zahirah (HSNZ) and the associated risk factors. **Methodology:** This case control study involved retrospective record review of all blood donors in HSNZ from 2011 until 2017. Seropositive donors were identified based on the positive serological tests. The data of blood donors were extracted from E-delphyn online system. The data on seropositive blood donors were extracted from the SUKUSA online system and donors' counseling records. For the association of the sociodemographic characteristics and the seropositivity, a group of randomly chosen seronegative blood donors were selected as the control group. Data were analysed using SPSS software version 24. **Results**: There was a total of 94,989 blood donations in HSNZ from 2011-2017, with majority of donations were Malays (91.6%), males (66.1%), students (53.4%), repeat donors (61.3%), and were from mobiles collection (84.7%). There was a total of 330 seropositive donations with the prevalence of 0.35%. HBV positivity constituted the highest prevalence (0.171%) followed by HCV (0.113%), syphilis (0.04%), and HIV

(0.024%). There were 13 seroconvert donors (0.014%) with the highest seroconversion was seen with HIV infection (5), followed by HCV (4), HBV (3) and syphilis (1). The majority of the identified risk factors among the seropositive blood donors were the unsafe sexual practices (51.7%), followed by having family history (38.3%), IVDU (8.3%) and previous history of transfusion (1.7%). These risk factors showed significant associations with all the TTI (p-values <0.05). The multiple logistic regression analysis showed that the odds of being seropositive were significantly higher in males compared to females, first time donors compared to repeat donors, occupation other than government servants compared to students and donation at mobiles compared to donation at centre respectively (p-values <0.05). **Conclusion**: The prevalence of seropositive and seroconvert blood donors in HSNZ were low with HBV was the most frequent infection. The most common associated risk factor was the unsafe sexual practice. Being male, first time donors, non-students, and donation at mobiles showed significantly higher risk of seropositivity.

(391 words)

Chapter 1

General Introduction

1.0 GENERAL INTRODUCTION

In the era of modern medicine, blood transfusion has become one of the measures used to manage patient, especially for those patients who have significant blood loss, or to increase oxygen carrying capacity in symptomatic anemic patients. On the other end of this practice, transfusion transmitted infection (TTI) is one of the concerned risks of blood transfusion (Adewoyin and Oyewale, 2015).

Various precautionary actions and measures had been implemented into the blood banking service in order to obtain a safer donor and reduce the infectious hazard for the patient through blood transfusion. Among these measures are promoting voluntary non-remunerated donors, repeated donations, self-deferral measures, strict donor selection and screening for specific infections on donated blood (World Health Organization, 2017). Screening for viral markers is very important, as measures such as self-deferral and strict donor selection are very subjective measures (Van der Bij *et al.*, 2006).

World Health Organization (WHO) recommends that all donated bloods were to be screened for at least four infections which are human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV) and *Treponema pallidum* (TP) spirochete for syphilis infection (WHO, 2017).

Serologic testing is an important measure to screen all the donated blood to make sure they are free from those four infections and safe to be transfused to the needed patients.

These serologic tests which comprise of antibody and/ or antigen assays, have helped tremendously in detecting infected donated blood, hence reducing the risk of TTI. However, there is still an issue regarding the long window period; the period during which the infected blood will be tested negative for the viruses (Kucirka *et al.*, 2011). Therefore today, nucleic acid testing (NAT) is performed in combination with serologic tests. In Malaysia, NAT has been implemented in the National Blood Centre (NBC) Kuala Lumpur since November 2007. Up to this date, the usage of this test has been expanded to cover all the states in Malaysia. NAT has significantly increased the sensitivity to detect infected blood components as it reveals viral agents earlier in the window period compared to the antibody or antigen assays (Nübling *et al.*, 2009; Hans and Marwaha, 2014).

Global status report on blood safety and availability 2016 by WHO stated that one of the indicators to monitor and evaluate the system of donor selection is by studying the confirmed seropositive blood donors. Therefore, evaluation of the trend in blood donors' infectious diseases rates is essential for monitoring the safety of blood supply and the effectiveness of donor screening. During the study period, samples from all donated blood in HSNZ were sent to NBC, Kuala Lumpur for serologic screening tests, but not yet for NAT. Therefore, there was still risk of releasing blood donated from donors who were in the window period, which had higher risk of TTI transmission (Sato *et al.*, 2001).

According to the Health Informatics Centre, Ministry of Health Malaysia, in the Health Indicator 2018, Terengganu is one of the states with high incidence rate of communicable diseases in 2017. The incidence rate of HCV in Terengganu (15.64 per

100 000 population) was higher compared to Malaysia's (9.54 per 100 000 population). In addition, the incidence rate of HBV (14.24 per 100 000 population) showed almost similar rate with national's incidence (15.41 per 100 000 population). However, up to this point of time, there is still no published data regarding seropositivity among blood donors in Terengganu generally and HSNZ specifically.

The purpose of this study was to: (i) determine the prevalence of seropositivity and seroconversion of HIV, hepatitis B, hepatitis C, and syphilis among blood donors, (ii) study the risk factors of the reactive blood donors, and (iii) compare the sociodemographic data between the seropositive and seronegative blood donors in HSNZ, Kuala Terengganu.

Chapter 2

Literature Review

2.0 LITERATURE REVIEW

2.1 Blood donation

2.1.1 Introduction

Blood donation is a process when a person voluntarily has blood drawn and the blood is used for transfusions to other person or to the donor him or herself. Blood donation may be of whole blood or of specific components directly by a process called apheresis donation. Blood donations can also be divided into groups based on who will receive the collected blood (British Committee for Standards in Haematology, 2007).

An allogeneic donation is when a donor gives blood for storage at a blood bank for transfusion to an unknown recipient. Today in the developed world, most of blood donations are of the allogeneic donations (WHO, 2017). An autologous donation is when a person has blood stored that will be transfused back to the donor later, usually during or after surgical procedure (Vanderlinde *et al.*, 2002). A directed donation on the other hand, is when a person, often a family member, donates blood for transfusion to a specific individual. Directed donations are relatively rare when an established supply exists (Wales *et al.*, 2005).

Apart from that, there is also 'replacement donor' donation, in which it involves combination of both the allogeneic and directed donation. It is common in developing countries such as Ghana (Addai-Mensah *et al.*, 2015). In this type of donation, a friend or family member of the recipient donates blood to replace the stored blood used in order

to ensure a consistent blood supply. Many donors donate as an act of charity but in countries that allow paid donation, some donors are paid, and in some cases there are incentives other than money such as time-off from work (Abolghasemi *et al.*, 2010).

2.1.2 Donor eligibility criteria

Information provided by 128 countries to the WHO Global Database on Blood Safety indicates that the median rate of total donor deferral was about 12% worldwide, with various reasons. These include anaemia, existing medical conditions or the risk of infections that could be transmitted through transfusion (WHO, 2017).

In reference to the Transfusion Practice Guideline for clinical and laboratory personnel (2016) by NBC, MOH Malaysia, each prospective donor must meet the following criteria in order to be eligible to donate:

a. Age
    - Between 17 to 65 years old.
    - First time donor can be accepted up to the age of 60 years old.
    - Regular donors can be allowed to donate up to the age of 65 years, provided they undergo and pass yearly medical examinations or produce an official letter from a qualified physician stating his or her fitness to donate.

b. Weight and haemoglobin level
    - The minimum weight for a whole blood donor shall be 45kg.
    - The minimum weight for an apheresis donor shall be 55kg.

- The haemoglobin level of a male donor shall be between 13.5g/dl and 18.0g/dl while for female donor between 12.5g/dl and 18.0g/dl.

c. Blood pressure.
    - The acceptable limits of blood pressure of the donor are:
        - 100 to 150mm Hg for systolic pressure, and
        - 70 to 100mm Hg for diastolic pressure.

d. Medical history
    - The blood collection centre must not accept as a donor of any person who is found to have any medical history that could cause harm to the donor during donation, or to the recipient of the donated blood.

e. Each prospective donor must be screened against the database in the central registry (e.g. SUKUSA- Sistem Pengumpulan Maklumat untuk Pusat Kutipan & Pusat Saringan) or records of any previous deferrals. Anyone who is permanently deferred should not be accepted as a donor.

f. High risk behaviour
    - Persons involved in any activity that put oneself at high risk of being infected with TTI shall not be allowed to donate and shall be permanently deferred from future donation.
    - Sexual partners of the above-mentioned persons shall also not be accepted as blood donors.

g. Frequency of donation
    - A donor is allowed a maximum of four whole blood donations in a period of 12 months, with a minimum interval of eight weeks between successive donations.

- A donor donating platelet and/or plasma via apheresis is allowed a maximum donation of a total volume of 15 liters, or 24 times in a period of 12 months, whichever comes first, with a minimum interval of two weeks between successive donations.

h. Specific criteria for foreigners (non-Malaysian citizen)

- A prospective donor who is a foreigner (non-Malaysian citizen) can be considered for donation only if he or she:
    - Has resided in Malaysia for at least 12 months.
    - Able to provide a residential or postal where the donor is contactable.
    - Must be able to read and understand Bahasa Malaysia or English.

The prospective donors should only be accepted if they appear to be in good health and comply with all the stated donor selection criterias. The selection of blood donors generally has two main purposes. The first is to protect recipients of blood transfusion from adverse effects such as TTI or other medical conditions and unwanted effects caused by medication taken by the donor. Secondly, to protect donors from potential harm which may occur as a direct result of the donation process (Kamel *et al.*, 2010).

2.1.3 Blood donation process

The quality and safety of blood and blood products must be assured throughout the process from the selection of blood donors to the administration of blood into the patient as described in the WHO Blood Safety Initiative 2017.

A blood donation process starts with selection of blood donors, in which WHO has clearly stated that the safest blood donors are voluntary, non-remunerated blood donors from low-risk populations. In order to fulfill the criteria of safe blood donors, there are few steps involved in the donor selection, which include pre-donation information, completion of donor questionnaire, health and risk assessment as well as pre-donation counseling (WHO, 2012).

Through the confidential questionnaire, donors are asked specific questions regarding lifestyle, health, medical and travel history to assure that they are in good health. These are to ensure that patient will receive safe blood products. Donors can be deferred for a variety of reasons (Transfusion Practice Guidelines, 2016):

- Signs and symptoms of infections.
- Social behaviours that increase their risk of exposure to infectious diseases. These include men who have sex with other men (MSM), intravenous drug use (IVDU) and exchanging sex for drugs or money.
- Travel to certain countries where the risk of exposure to a particular infectious disease is of concern.
- Medical procedures that involve receipt of dura mater graft.
- Transfusion of blood or blood components within the previous 6 months.

- Obtaining a piercing or tattoo using nonsterile materials within the previous 6 months.
- Certain medications and immunizations.
- Pregnancy.

In Malaysia, self-deferral is one of the important steps in donor screening procedure. Self-deferral is a process in which an individual who identifies him or herself as potentially carrying a higher risk of a TTI and chooses not to donate blood for some reasons (Lee *et al.*, 2013). Individuals who belong to any of the high-risk groups are encouraged to self-defer to ensure the safety of blood supply. It is harmful to a blood transfusion recipient if the individual donates during the window period. This is because serological tests are less likely to detect the infection during a window period donation. Thus, the donated blood might be used for transfusion and infecting the recipient (Lee *et al.*, 2014).

The system of confidential unit exclusion (CUE) offers donors the opportunity to inform the blood transfusion service immediately after donation or subsequently if they consider that their blood may be unsafe for transfusion. This may be particularly useful if donors have been persuaded to donate. The CUE system is designed to add an additional level of safety to the donor selection and blood screening processes and has been found to be effective in some settings (Lee *et al.*, 2005). However, there were some evidence that it may have limited effect on reducing the transmission of infections through window-period donations and may lead to the discard of safe donations (Zou *et al.*, 2004; O'Brien *et al.*, 2010).

While the donor questionnaire and interview process are intended to elicit relevant information on which to assess donor suitability for blood donation, the process sometimes may not be effective. A surveillance program installed in Netherland found that nearly 25 percent of the seropositive donors did not report factors at screening that would have deferred them from donating blood (Van der Bij *et al.*, 2006). Therefore, screening for viral markers is very important since measures such as self-deferral and strict donor selection are very subjective. The overall process of donor screening and selection was summarized in Figure 2.1.

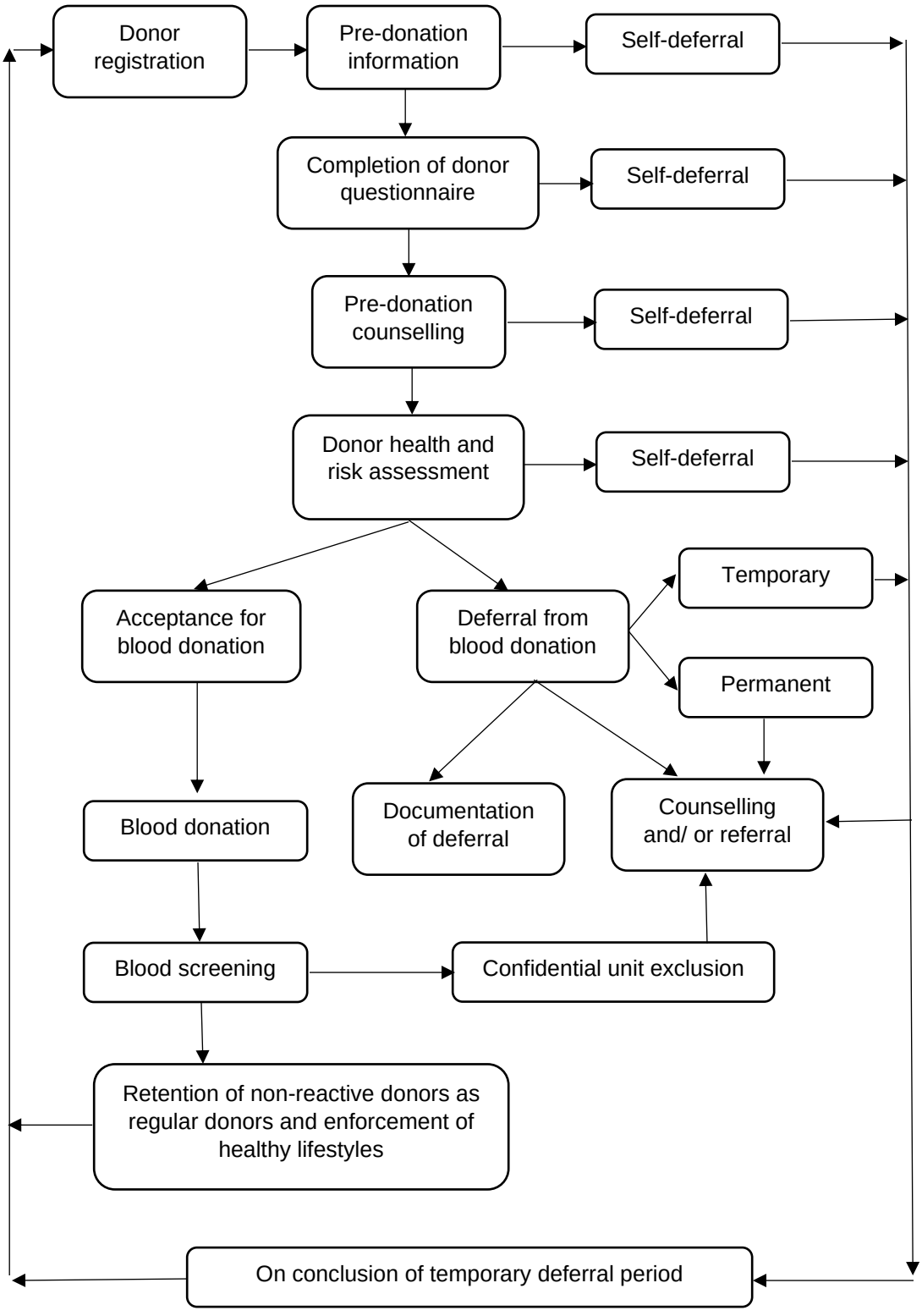

Figure 2.1: The blood donor selection process (Adapted from WHO, 2012)

2.1.4 Serology testing of TTI

WHO recommends that at a minimum, screening of all blood donations should be mandatory for the following infections and using the following markers (WHO, 2010):

i. Hepatitis B: screening for hepatitis B surface antigen (HBsAg)
ii. Hepatitis C: screening for either a combination of HCV antigen-antibody or HCV antibodies
iii. HIV-1 and HIV-2: screening for either a combination of HIV antigen-antibody or HIV antibodies
iv. Syphilis (*Treponema pallidum*): screening for specific treponemal antibodies

In Malaysia, the markers used are HBsAg, HCV antibodies, HIV antigen-antibody and antibodies toward TP. Nowadays, NAT has been added as a complement test to these serological tests, to increase the probability of TTI detection (Chaurasia *et al.*, 2014).

2.1.5 TTI screened in Malaysia

a) HIV

The first case of HIV in Malaysia was documented more than 25 years ago and currently, there are more than 81 000 people living with HIV in the country (Barmania, 2013). HIV can be transmitted via multiple routes which include transmission through unprotected and close contact with a variety of body fluids of infected individuals. Patel *et al.* (2014) reported that HIV transmission was greatest for blood transfusion, followed by vertical exposure, sexual exposure and other parenteral exposures. Infectivity estimates in case of transfusion of infected blood products are much higher (around 95%) than for other modes of HIV transmission owing to the much larger viral load per exposure compared to other routes. Therefore, the detection of this infection in blood donors is extremely important, in order to prevent transmission (Baggaley *et al.*, 2006).

b) Hepatitis B

Hepatitis B is a potentially life-threatening liver infection caused by the HBV. The virus can be transmitted from human to human via blood or body fluids. Consequently, it may be transmitted by transfusion or transplantation, via needles and other items exposed to blood. This virus can also be transmitted from mother to child in utero, at birth or perinatally (Pereira *et al.*, 2002; Weinbaum *et al.*, 2008; Goldman *et al.*, 2009). The incubation period of the HBV is 90 days on average. However, it can vary from 30 to 180 days. Most people do not experience any symptoms during the acute infection phase. The virus may be detected 30 to 60 days after infection and persists for variable periods of time (Kim *et al.*, 2011).

Malaysia is a country of medium seroprevalence for HBsAg in the general population (1.5-9.8%) with estimated 1 million people are chronically infected with hepatitis B (Yap, 1994). Since the introduction of hepatitis B vaccination program for children in 1989, the seroprevalence of infection among Malaysians was successfully reduced (Raihan, 2016). However, disease burden remained high for some time as the infected people are getting older. It is crucial to detect individuals with this infection to avoid transmission. Therefore, all HBsAg positive donors should be considered at high risk of transmitting HBV thus should be deferred from blood donation. A deferral period of 12 months from recovery is generally recommended by the WHO. The suitability to donate blood is assessed based on the results of testing for HBsAg, hepatitis B core antibody (anti-HBc) and antibody to hepatitis B surface antigen (anti-HBs) levels (Taira *et al.*, 2013).

c) Hepatitis C

Hepatitis C is a liver disease caused by HCV. The HCV is most commonly transmitted through exposure to infectious blood (Rehan *et al.*, 2011). This can occur through contaminated blood transfusions, blood products or organ transplants. Transmission can also occur through injections given with contaminated syringes, needlestick injuries in health-care settings or injecting drug use. Apart from that, this virus can also be transmitted perinatally from a hepatitis C-infected mother or through sex with an infected person (Nguyen *et al.*, 2010; Indolfi *et al.*, 2013). Less commonly, sharing of personal items contaminated with infectious blood can also cause viral transmission (Yang *et al.*, 2014).

The incubation period for hepatitis C is two weeks to six months. Following initial infection, approximately 80% of people do not exhibit any symptoms (Maasoumy and Wedemeyer, 2012). During this window period, serological test might show negative result if the donor is allowed to donate. Owing to the variable length of the window period, viral NAT plays an important role to detect the infection earlier and subsequently prevent the transmission of HCV through infected blood products (Li *et al.*, 2008).

d) Syphilis

Syphilis is one of the common sexually-transmitted diseases which is caused by TP spirochete. It should be noted that a history of sexually transmitted disease is an important indicator for sexual behaviours associated with HIV transmission. Therefore, controlling sexually transmitted infections is important for preventing HIV infection, particularly in people with high risk sexual behaviours (Adolf *et al.*, 2012).

Comparing to other TTI, the risk of transmission of syphilis through the transfusion of processed and stored blood is low as the spirochetes are released into the bloodstream only intermittently during the course of infection. In addition, these spirochetes are destroyed within 5 days of storage at 4˚C. However TP can be transmitted through transfusion of fresh blood (Owusu-Ofori AK, 2011).

2.2 Seropositive blood donors

2.2.1 Prevalence of seropositive blood donors

Generally, the prevalence of TTI in blood donations in high-income countries is considerably lower than in low- and middle-income countries, as shown in Table 2.2. These differences reflect the variations in prevalence among population who are eligible to donate blood, the type of donors (such as voluntary unpaid blood donors from lower risk populations) and the effectiveness of the system of educating and selecting donors (WHO, 2017).

Table 2.1: Prevalence of transfusion-transmissible infections in blood donations (median, (interquartile range)), by income groups. (Adapted from WHO, 2017)

	HIV	HBV	HCV	Syphilis
High-income countries	0.002% (0.004% – 0.02%)	0.02% (0.008% – 0.08%)	0.02% (0.005% – 0.11%)	0.02% (0.006% – 0.14%)
Upper middle-income countries	0.10% (0.02% – 0.22%)	0.36% (0.18% – 0.73%)	0.24% (0.05% – 0.38%)	0.44% (0.12% – 1.09%)
Lower middle-income countries	0.14% (0.03% – 0.6944%)	2.27% (0.80% – 4.87%)	0.39% (0.18% – 0.95%)	0.70% (0.19% – 1.27%)
Low-income countries	0.86% (0.39% – 2.40%)	3.64% (2.55% – 8.59%)	0.93% (0.50% – 1.95%)	0.60% (0.30% – 1.63%)

Studies that were done worldwide showed a variable prevalence of all the TTI which were screened among blood donors. A retrospective analysis of consecutive blood donors' records done in a university teaching hospital in Ethiopia from 2003 to 2007 found that the overall seroprevalence of HIV, HBV, HCV and syphilis was 3.8%, 4.7%, 0.7%, and 1.3% respectively (Tessema *et al.*, 2010).

Another retrospective analysis (2010-2014) among consecutive, voluntary blood donors in Shiyan City, Central China, found that the seroprevalence of HIV, HBV, HCV and T. pallidum were 0.08 %, 0.51 %, 0.20 % and 0.57 %, respectively (Yang *et al.*, 2016). A retrospective analysis (2013-2015) among donors in Kyrgyzstan found that the prevalences of HBsAg, anti-HCV, HIV and anti-TP were 3.6%, 3.1%, 0.78% and 3.3%, respectively. From 2012 to 2015, there was a decreasing trend in the seroprevalence of HBsAg, anti-HCV, and anti-TP, while the seroprevalence of HIV was increased (Karabaev *et al.*, 2017).

Other than that, another study in Delhi showed donors' seropositivity for HIV and VDRL was 0.54% and 2.6% respectively (Singh *et al.*, 2005), while a study on Lao blood donors found that the seroprevalence of HBsAg and anti-HCV positive blood donors was 8.7% and 1.1% respectively (Jutavijittum *et al.*, 2007).

2.2.2 Factors associated with seropositive blood donors

Studies done at different parts of the world reported different outcomes in terms of risk factors of seropositivity. In Ethiopia, Tessema *et al.* (2010) reported that the seropositivity of HIV was significantly increased among female blood donors, first time donors, housewives, merchants, soldiers, drivers and construction workers. Significantly increased HBV seropositivity was observed among farmers, first time donors and age groups of 26 - 35 and 36 - 45 years. Similarly, the seroprevalence of syphilis was significantly increased among daily labourers and construction workers.

Another study in China found that the HIV and syphilis seropositivities significantly increased among female donors and farmers. Significantly increased HBV seropositivity was only observed among farmers compared to workers. Analogously, significantly increased HCV seropositivity was observed among farmers, students, merchants and other. In addition, significantly increasing trends of HIV, HBV, HCV, and syphilis seropositivities were observed over the study period (Yang *et al.*, 2016).

Other than that, a study in Pakistan showed an increase in the prevalence of HCV infection in blood donors from interior Sindh between 2004 and 2007. On the contrary, decreasing prevalence of HBV was found, particularly in literate blood donors within the same time frame (Mujeeb and Pearce, 2008).

Besides, a study on Lao blood donors found that the seroprevalence of HBsAg positive blood donors was higher among males. On the other hand, the prevalence of anti-HCV positive blood donors showed no significant differences between male and female blood donors (Jutavijittum *et al.*, 2007).

Another study among Thai blood donors revealed four variables related to HCV infection among the studied samples, which were education up to primary level, occupation as a laborer or agriculture worker, a history of receiving blood or blood products and a history of intravenous drug user (Luksamijarulkul *et al.*, 2004).

In Kyrgyzstan, reported that males were more likely to be seropositive for HBsAg than females, but less likely to be seropositive for anti-HCV and HIV. It was also reported that level of donors' awareness regarding high risk behaviour can lead to higher risk of TTI. Repeat blood donors with high risk activities were more likely to have seropositive results for HBV, HIV and Syphilis. Sociodemographic factors such as male and working in the private sector predominated in all TTI markers (Karabaev *et al.*, 2017).

2.2.3 TTI and high risk behaviours

a) High risk sexual behaviours

Certain sexual behaviours have been shown by surveillance data to be associated with a high risk of transmission of HIV, HBV and HCV. Therefore, it is essential to identify and defer from blood donation, individuals whose sexual behaviour puts them at high risk of acquiring infectious diseases that can be transmitted through blood (Musto *et al.*, 2008).

High-risk sexual behaviours include having multiple sex partners, receiving or paying money or drugs for sex, including sex workers and their clients, men having sex with men (MSM) and females having sex with MSM (Johnson *et al.*, 2003; Beyrer *et al.*, 2011). MSM accounts for the largest subpopulation of HIV-infected people in most developed countries (Wainberg *et al.*, 2010; Pedrana *et al.*, 2012). Hence, deferring permanently men who have ever had oral or anal sex with another man is crucial (Benjamin *et al.*, 2011).

b) Injecting drug users

The use of injected 'recreational' drugs and non-prescribed steroids are commonly associated with unsafe practices such as the sharing and re-use of needles. It carries a high risk of blood-borne infections most commonly HCV, but also HBV and HIV (Baldo *et al.*, 2008; Salmon *et al.*, 2009). Many injected drugs are highly addictive and their use may be life-long. Therefore, the safest policy is permanent deferral of anyone who has ever injected non-prescribed drugs (Nash *et al.*, 2009).

c) Cosmetic treatments and rituals

Any procedures involving penetration of the skin carry a risk of bloodborne infections, especially HIV, HBV and HCV, unless performed under sterile conditions. These include body piercing, tattooing, scarification, injections with collagen or botulinum toxoid (botox), electrolysis and semi-permanent make-up (Oberdorfer *et al.*, 2003; Hwang *et al.*, 2006).

2.3 Seroconvert blood donors

A seroconvert donor is a repeat donor who is confirmed positive for a particular TTI in his current donation but was negative in the previous donation. The number of donors who seroconvert between donations is needed to estimate the risk of collecting a donation from a recently infected donor who has not yet developed detectable markers, hence the risk of transmitting the infection by transfusion (Kleinman and Secord, 1988). Therefore, in any case of seroconvert donor, a lookback procedure must be initiated. In this procedure, the recipients of all seronegative donations within the 6 months period previous to the last seronegative donation were traced. The hospitals or wards who received blood components from a pre-seroconversion donation were informed and advised to trace the recipient for testing. This illustrates that a single seroconvert donor could rise a serious impact in the patient's management (Byrne *et al.*, 2011).

A cross sectional study conducted in National Blood Centre, Kuala Lumpur in 2010, found that there was a total of 0.064% seroconversion rate among repeat donors in 5-year time (2004-2008). Among that, syphilis accounted for the highest and increasing seroconversion rate from 20.83% in year 2004 to 44.6% in year 2008. HIV and HCV

infection also showed increasing seroconversion rate in 5 years' time from 6.41% in year 2004 to 17.54% in year 2008 and 4.8% in year 2004 to 5.94% in year 2008 respectively. However, HBV infection alone showed a decreasing seroconversion rate from 20.83% in year 2004 to 10.4% in year 2008 (Nafishah *et al.*, 2014).

Studies done in other countries generally reported a low prevalence of seroconvert blood donors. A study which was done in the state of Para, Brazil showed that among the 157,432 donations from 2008 to 2010, 45 HIV seroconversions were confirmed. Of these, majority were men, single, had completed high school and were between 23 and 29 year-old (Costa and Brasiliense, 2011). An earlier study done in 14 blood centres in England reported an estimated seroconversion rate of 0.26 per 100 000 person years for HCV infection (Soldan *et al.*, 1998).

The introduction of NAT is one of the initiatives done to reduce the seroconversion rate among blood donors. Studies have shown that the application of NAT had tremendously shortened the window period of TTI thus resulted in better detection of the infections (Dodd *et al.*, 2002; Stramer *et al.*, 2004; Assal *et al.*, 2009).

2.4 Blood transfusion practice

2.4.1 Introduction

Blood transfusion is an important aspect in clinical practice. Factors such as advances in surgeries and treatment, tightening of the blood donation criteria, seasonal shortages of blood supply, and aging of the blood donor populations have cause increasing blood demands (Gilcher and McCombs, 2005).

The major concerns from the point of view of both, the patients and the clinicians are for safe, effective and quality blood to be available when it is required. Therefore, standard practices should be in place. These include careful selection of blood donors, screening of donations, proper storage of donated blood, appropriate use of blood supplied and reports of transfusion reactions. Blood for transfusion is considered safe when it is donated by a carefully selected healthy donor, free from infections that could be harmful to the recipient, processed by reliable methods of testing, appropriately stored before being issued and transfused only upon need (WHO, 2008).

The collected blood from a donor could be mixed with anticoagulant in the collection bag and stored in an unmodified state. The transfusion of these type of blood is known as whole blood transfusion. On the other hand, the collected blood can be used more effectively if it is processed into components. These include red cell concentrates, platelet concentrates, plasma and cryoprecipitate. In this way, it can meet the needs of more than one patient. It is reported that 85% of whole blood donations collected globally were processed into components (Devine and Howe, 2010).

2.4.2 Principles and indications of blood transfusion

Transfusion of blood and blood products should be undertaken only to treat a condition that would lead to significant morbidity or mortality and that cannot be prevented or managed effectively by other means. Most people cope well with losing a moderate amount of blood (< 20 – 30% of body volume) and this should be replaced by crystalloids or colloids. Medication such as iron may help to compensate for the blood loss but if a large amount is lost, then blood transfusion is the best way to replace it rapidly (Holm *et al.*, 2017). A brief summary of indications of blood transfusion is given in table 2.1 (Yaddanapudi and Yaddanapudi, 2014).

Table 2.2: The clinical indications of blood transfusion

Clinical condition	Transfusion trigger	Reference
Acute anaemia		
Surgical haemorrhage	Hb ≤8 g/dL or symptomatic*	Carson *et al.*, 2012
Traumatic haemorrhage	Haemorrhagic shock, inadequate oxygen delivery	Napolitano *et al.*, 2009
Critical illness	Hb <7 g/dL or symptomatic*	Napolitano *et al.*, 2009
Septic shock	Hb <7 g/dL	Retter *et al.*, 2013
Acute coronary syndrome	Hb 8-9 g/dL	Retter *et al.*, 2013
Chronic anaemia		
Chronic blood loss	No clear-cut transfusion triggers have been defined.	Shander *et al.*, 2013
Decreased erythropoiesis		

*Symptoms of anaemia include symptoms of myocardial ischemia, and orthostatic hypotension or tachycardia unresponsive to fluids

2.4.3 Adverse effects of blood transfusion

In general, transfused red blood cells provide three beneficial effects. These include circulatory (volume-related), rheological (viscosity-related) and oxygen carriage (Shander *et al.*, 2013). However, despite the mentioned benefits of blood transfusion to the recipients, there were also reported adverse effects of this therapy. These unwanted effects are called transfusion reactions and can be divided into acute or delayed reactions. These can further be divided into either immunologic or nonimmunologic reactions. Among these adverse reactions of blood transfusion, transmission of infectious diseases has been described as one of the possible delayed non-immunologic reactions, as shown in Figure 2.2 (Adewoyin and Oyewale, 2015).

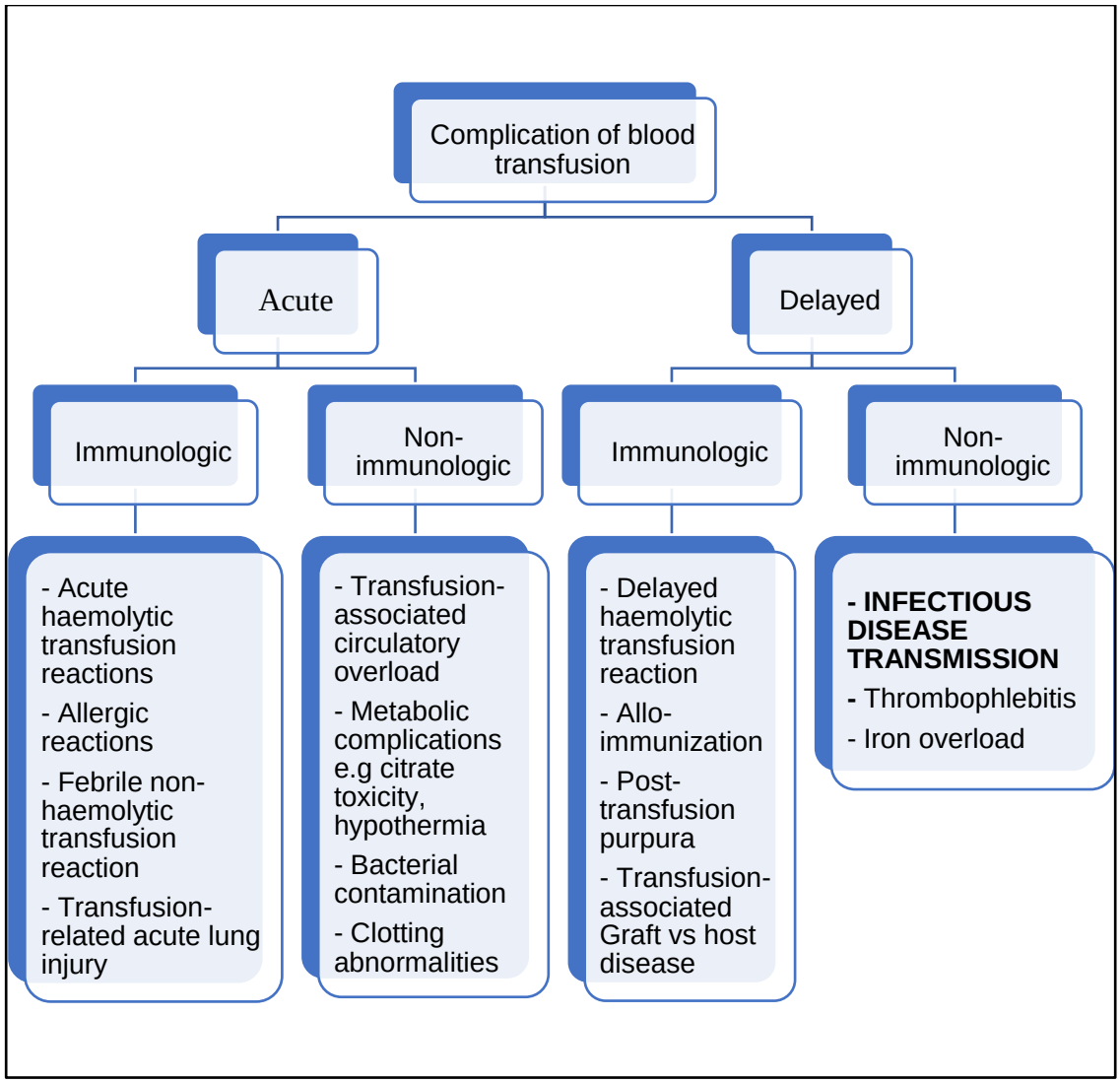

Figure 2.2: Complications of blood transfusion

2.5 Haemovigilance in blood transfusion

Haemovigilance is defined as a set of surveillance procedures covering whole transfusion chain from the collection of blood and its components to the follow-up of its recipients. It is intended to collect and access information on unexpected or undesirable effects occured either to the donors and the recipients of the blood products, and to prevent their occurrence and recurrence (De Vries *et al.*, 2011).

Donor haemovigilance is a surveillance system to track adverse events associated with blood donation with the intention to improve the safety of the donation process. This system allows the collection centre to monitor the prevalence of adverse donor events, its trends and find ways to improve blood donation process. This resulted in high quality donor care and safety thus better donor return (NBC, 2016).

The online system called SUKUSA (Sistem Pengumpulan Maklumat Pusat Kutipan & Pusat Saringan) served as one of the important tools in detecting donors who had been deferred permanently during previous donation screening. This could prevent them from further donation and thus, reduce the seropositive donations. This online system could be accessed by all blood donation centers including in mobiles setting. Donor database or registry were proven to be beneficial especially in the management of seropositive donor or donors with high risk behaviours (Edgren *et al.*, 2006).

Patient haemovigilance is a surveillance system that monitors the transfusion process in the clinical area. This includes the monitoring of adverse transfusion reactions. Information about any adverse effects in the recipients of transfusion also fed back into the donor haemovigilance system in order to improve donor selection in the future (NBC, 2016).

Chapter 3

Objectives

3.0 OBJECTIVES

3.1 General objective

To study the seropositivity of HIV, hepatitis B, hepatitis C, and syphilis among blood donors at Hospital Sultanah Nur Zahirah (HSNZ), Kuala Terengganu.

3.2 Specific objectives

i. To determine the prevalence of seropositive blood donors of HIV, hepatitis B, hepatitis C and syphilis in HSNZ.
ii. To determine the prevalence of seroconversion of HIV, hepatitis B, hepatitis C and syphilis among blood donors at HSNZ.
iii. To identify the risk factors for tested transfusion transmissible infection among the seropositive blood donors at HSNZ.
iv. To compare the sociodemographic characteristics between the seropositive and seronegative blood donors at HSNZ.

Chapter 4

Methodology

4.0 METHODOLOGY

4.1 Study design

4.1.1 Study design for objective i, ii, and iii

This study was a cross sectional study with retrospective data collection, conducted over one year from January 2018 till December 2018 at HSNZ, Kuala Terengganu.

4.1.2 Study design for objective iv

This involved case control study, conducted over the same period of time and at the same centre.

4.2 Sampling method

4.2.1 Source population

The source population of the subjects were the blood donors in HSNZ, Kuala Terengganu.

4.2.2 Sampling frame

The sampling frame were those blood donors in HSNZ who fulfilled the inclusion and exclusion criteria.

4.2.3 Inclusion criteria

All blood donors in HSNZ, including the first time and repeat blood donors. Those who were found to have false positivity were regarded as seronegative blood donors.

4.2.4 Exclusion criteria

Non-citizen blood donors were excluded from the study.

4.2.5 Sampling of cases and controls

All blood donors at HSNZ within the period of 2011 to 2017 who fulfilled the inclusion and exclusion criteria were included in the study. All seropositive donors within the specified period were included for further study on their risk factors and the sociodemographic characteristics. The seroconvert blood donors were identified among the seropositive blood donors.

A group of randomly chosen seronegative blood donors were also selected and evaluated for the same demographic characteristics studied as the control group. This control groups were selected randomly using Microsoft Excel, based on year and month of donation.

4.3 Sample size calculation

4.3.1 Sample size calculation for objective i, ii, and iii

- Using the single proportion formula,

  α = 0.05, thus Zα = 1.96

  Δ = 0.005%

  P = 1.4% (Yang S. et al, 2016)

- $n= (1.96/0.005)^2$ X 0.014(1-0.014) = 2 121
- Drawback 10%= 212
- Total sample size= **2 333**

4.3.2 Sample size calculation for objective iv

- Using Power and sample size calculation software, the two proportion formula for case control study,
  - P0 = the probability of exposure in controls.
  - P1 = the probability of exposure in cases.
  - Power = the probability of correctly rejecting the null hypothesis
  - α = 0.05 (the probability that will falsely reject the null hypothesis).

Demographic characteristics	P0	P1	Power	m	Sample size	Sample size x 2
1. Gender	0.80 (seronegative male donors) (Tessema *et al.*, 2010)	0.95 (seropositive male donors)	0.8	1	75	150
2. Age	0.40 (seronegative donors aged <45) (Tessema *et al.*, 2010)	0.60 (seropositive donors aged <45)	0.8	1	97	194
3. Occupation	0.03 (seronegative unemployed donors) (Tessema *et al.*, 2010)	0.23 (seropositive unemployed donors)	0.8	1	43	86
4. Number of donation	0.70 (seronegative first time donors) (Tessema *et al.*, 2010)	0.90 (seropositive first time donor)	0.8	1	62	124

Final sample size= 194 + 10% drawback= **213**

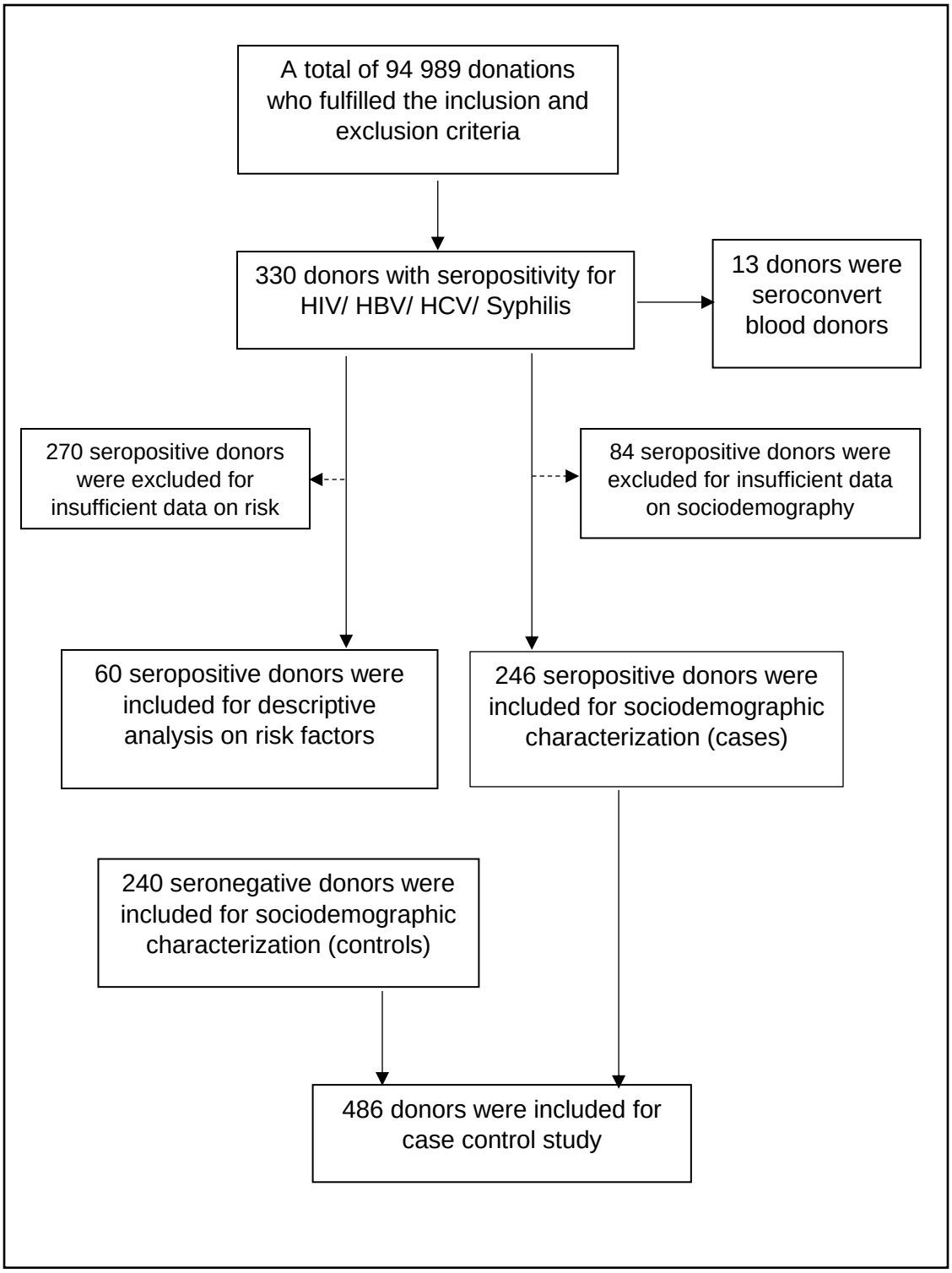

Figure 4.1: Flow diagram of the sample selection

4.4 Data collection

Data on all blood donors in HSNZ were obtained from the blood bank registry, including the number and site of donations. Further details of the confirmed seropositive blood donors were also gathered from the registry in the blood bank, both from the online registry and manual records in the blood bank. The sociodemographic characteristics (including age, gender, marital status, occupation, number of donation, and donation site) and the risk factors were extracted from online database and donors' counseling records. The collected data was documented in the data collection form (Appendix A).

The results of the serology tests for the HIV, HBV, and HCV infections were received from National Blood Centre (NBC) Kuala Lumpur, as all the blood donors' sample were sent and analyzed there for these three infections. For syphilis infection, the serology test was done in the transfusion microbiology laboratory (TML), HSNZ. The serology tests done included both the screening and the confirmatory tests. The results were considered as confirmed seropositive if:

- For HIV: The repeatedly reactive sample on enzyme immunoassay (EIA) was found to be positive on line immunoassay (LIA) method.
- For HBV: The repeatedly reactive sample on EIA was found to be positive on Neutralization test.
- For HCV: The repeatedly reactive sample on EIA was found to be positive on LIA method.
- For syphilis: The repeatedly reactive sample by rapid plasma regain (RPR) test was found to be positive with treponema pallidum particle agglutination (TPPA) method

The repeatedly reactive sample referred to the donation sample that was also found to be reactive on the duplicate sample of the pilot tube, tested using the same analyser.

4.5 Laboratory method

4.5.1 HIV

a) Screening test: Enzyme immunoassay (EIA)

The general principle of EIA or also known as enzyme-linked immunosorbent assay (ELISA) involved the use of enzyme conjugates that bind to specific HIV antibody, and substrates or chromogens that produce color in a reaction catalyzed by the bound enzyme-conjugate. The newer generation of combination ELISAs that simultaneously detect both antigen and antibody were now been used widely, and offers advantages for decreasing the time, personnel, and costs necessary to perform each assay individually. These assays demonstrated a high analytical sensitivity of detection that was most likely attributed to the combination of a third-generation format (antigen sandwich) for antibody detection and the ability to simultaneously detect HIV p24 antigen (Buttò *et al.*, 2010).

The most popular ELISA involved an indirect method in which HIV antigen is attached to a well of a microtiter plate. Antibody in the sample was allowed to react with the antigen-coated solid support. After a wash step to remove unbound serum components, addition of a conjugate, bound to the specific antibody that was attached to the antigens on the solid phase. Following another wash, addition of an appropriate substrate resulted in color development that was detected by a spectrophotometer and was proportional to specific HIV antibody concentration in the sample. Optical density (OD) values were

produced as the colored solution absorbs transmitted light, and provide an indication of the amount of color, which was proportional to the amount of antibody bound (i.e. antibody concentration). A mathematical calculation, usually based on the OD of the negative controls multiplied by a factor, produced a cut-off value on which the OD of the sample was compared to determine the antibody status; samples with OD cutoff values >1.0 (in an indirect ELISA) were considered antibody reactive (Nishanian *et al.*, 1987).

b) Confirmatory test: Line immunoassay (LIA)

The LIA is an alternative test to the classic Western blot confirmatory tests. In this assay, recombinant or synthetic peptide antigens were applied on a nitrocellulose strip, rather than electrophoresed as in the Western blot. This use of artificial antigens decreased the presence of contaminating substances derived from cell culture that can cause interference and sometimes false reactions (Constantine and Zink, 2005).

In this assay, the recombinant proteins and synthetic peptides from HIV-1 and HIV-2, and a synthetic peptide from HIV-1 group O were coated as discrete lines on the nitrocellulose strip. Five HIV-1 antigens were applied: sgp120 and gp41, which detect specific antibodies to HIV1, and p31, p24, and p17, which may also cross-react with antibodies to HIV-2. HIV-1 group O peptides were present in the HIV-1 sgp120 band. The antigens gp36 and sgp105 were applied to detect antibodies to HIV-2. In addition to these HIV antigens, control lines were also coated on each strip: antistreptavidin line, ± cut-off line (human IgG), 1+ positive control line (human IgG) and one strong 3+ positive control line which was also the specimen addition control line (anti-human IgG). The test specimen was then incubated in a test trough together with the multiple antigen-coated

test strip. HIV antibodies, if present in the specimen, bind to the individual HIV antigen lines on the strip. Afterwards, an anti-human immunoglobulin (IgG) labelled with alkaline phosphatase was added and bind to any HIV antigen-antibody complex previously formed. Incubation with enzyme substrate produced a dark brown color in proportion to the amount of HIV antibody present in the specimen. If the specimen contains no HIV-specific antibodies, the labelled antihuman antibody will not be bound to antigen-antibody complex so that only a low standard background color developed.

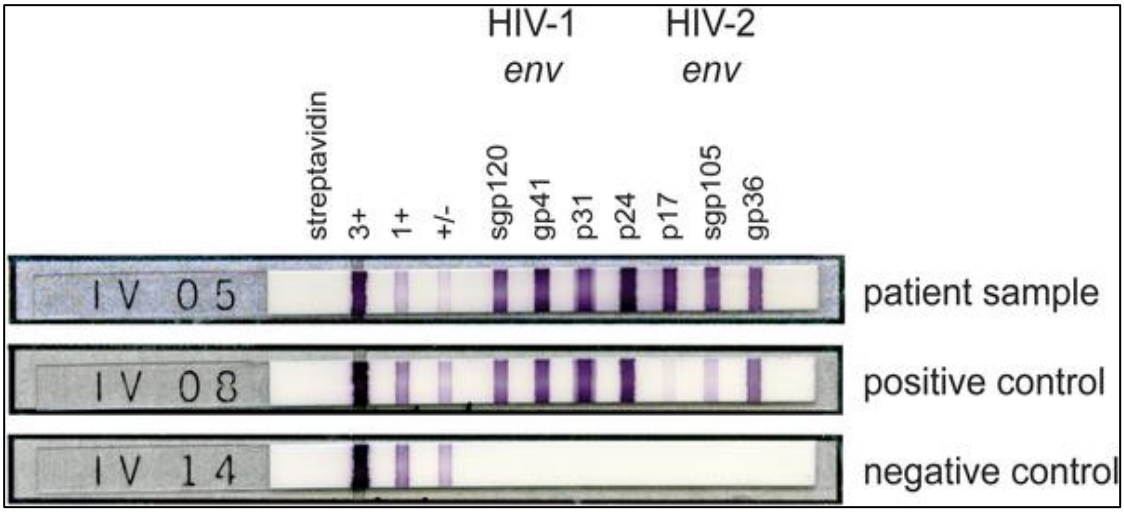

Figure 4.2: Line immunoassay showing seropositivity for both HIV-1 and HIV-2 (Adapted from Zbinden *et al.*, 2016)

4.5.2 Hepatitis B virus (HBV)

Hepatitis B surface antigen (HBsAg), are produced in excess by the HBV during its infection. This antigen is the first serological marker after infection, appearing one to twelve weeks after exposure and two to eight weeks before the onset of clinical symptoms. It is responsible for binding the virus to the liver cells and is the target structure of neutralizing antibodies (Liang, 2009).

a) Screening test: EIA

This test was done for qualitative detection of HBsAg in the donors' serum/ plasma. In immunoassay using chemiluminescent technology, the test was done by combining the sample, anti-HBs coated microparticles and anti-HBs labeled conjugate, to create a reaction mixture. HBsAg which was present in the sample bound to the anti-HBs coated microparticles and to the labeled conjugate. After washing and addition of pre-trigger and trigger solutions to the reaction mixture, the resulting chemiluminescent reaction was measured as reactive light unit (RLU) (Shinkai *et al.*, 2013).

There is a direct relationship between the amount of HBsAg in the sample and the RLUs detected. The presence or absence of HBsAg in the sample was determined by comparing the chemiluminescent signal in the reaction to the cut-off signal determined from an active calibration. If the chemiluminescent signal in the specimen was greater than or equal to the cut-off signal, the sample was considered reactive for HBsAg.

b) Confirmatory test: Neutralization test

The HBsAg confirmatory assay uses the principle of specific antibody neutralization to confirm the presence of HBsAg.

The confirmatory reagent (human antibody to HBsAg) was incubated with the specimen in solution. If HBsAg was present in the specimen it will be bound by the confirmatory reagent. The neutralized HBsAg was subsequently blocked from binding to the antibody-coated bead. This resulted in a reduction of signal when compared to the non-neutralized specimen in which the negative control was used in place of the confirmatory reagent. A specimen is confirmed as positive if the reduction in signal of the neutralized specimen is at least 50% and the non-neutralized control generates a signal greater than or equal to the assay cut-off (Fletcher *et al.*, 2010).

4.5.3 Hepatitis C virus (HCV)

a) Screening test: EIA

Qualitative determination of the human antibody directed against HCV (anti-HCV) in human serum or plasma is measured using direct solid-phase enzyme immunoassay or its newer variation, the chemiluminescent immunoassay (Gupta *et al.*, 2014).

In chemiluminescent microparticle immunoassay, the sample, recombinant HCV antigen-coated microparticles, and labeled conjugate were combined to create a reaction mixture. Following addition of pre-trigger and trigger solutions, chemiluminescent reactions produced. This reaction was measured as RLU, which has direct relationship

with the amount of anti-HCV in the sample. The presence or absence of anti-HCV in the specimen was determined by comparing the chemiluminescent signal in the reaction to the cut-off signal and were interpreted in similar way as described in the HBsAg assay.

b) Confirmatory test: LIA

This is an in vitro qualitative enzyme immunoassay for the detection of anti-HCV in human serum or plasma. Detection of anti-HCV by LIA methodology is based upon traditional Western and dot blotting techniques, in which specific immunogens (i.e. antigenic polyproteins) encoded by the HCV genome were immobilized onto a membrane support. Visualization of anti-HCV reactivity in specimens to the individual HCV-encoded proteins was accomplished using anti-human IgG enzyme-conjugates in conjunction with a colorimetric enzyme substrate (Maertens *et al.*, 1999).

4.5.4 Syphilis

a) Screening test: Rapid Plasma Reagin (RPR)

The RPR 18-mm circle card test is a macroscopic, nontreponemal flocculation card test used to screen for syphilis. The antigen was prepared from a modified Venereal Disease Research Laboratory (VDRL) antigen suspension containing choline chloride to eliminate the need to heat-inactivate serum, ethylenediaminetetraacetic acid (EDTA) to enhance the stability of the suspension, and finely divided charcoal particles as a visualizing agent. In this test, the RPR antigen was mixed with serum or plasma on a plastic-coated card.

The RPR test measured IgM and IgG antibodies to lipoidal material released from damaged host cells as well as to lipoprotein-like material, and possibly cardiolipin released from the treponemes. If antibodies were present, they combined with the lipid particles of the antigen, causing them to agglutinate. If antibodies were not present, the test mixture was uniformly gray. The quantitative test will be performed on any sample showing any degree of reactivity. In the quantitative test, the reactive specimens were diluted serially with saline, while using the same test principle as the qualitative test. This RPR test were interpreted as reactive or non-reactive based on the presence or absence of the characteristic clumping. In the quantitative test, the results were given in the highest dilution that had given a reactive result (Alhabbab, 2018).

b) Confirmatory test: *Treponema pallidum* antibodies

The qualitative detection of antibodies to *Treponema pallidum* (TP) antigens was done using immunochromatographic test in HSNZ. This test was done by adding sample to the sample pad. As the sample migrated through the conjugate pad, it reconstituted and mixed with the TP antigen-selenium colloid conjugate. This mixture continued to migrate through the solid phase to the immobilized TP antigens at the patient window site. If antibodies to TP were present in the sample, the antibodies bind to the TP antigen-selenium colloid and to the TP antigen at the patient window, forming a red line at the patient window site. If antibodies to TP were absent, the TP antigen-selenium colloid flew past the patient window, and no red line was formed at the patient window site (Lee *et al.*, 2015).

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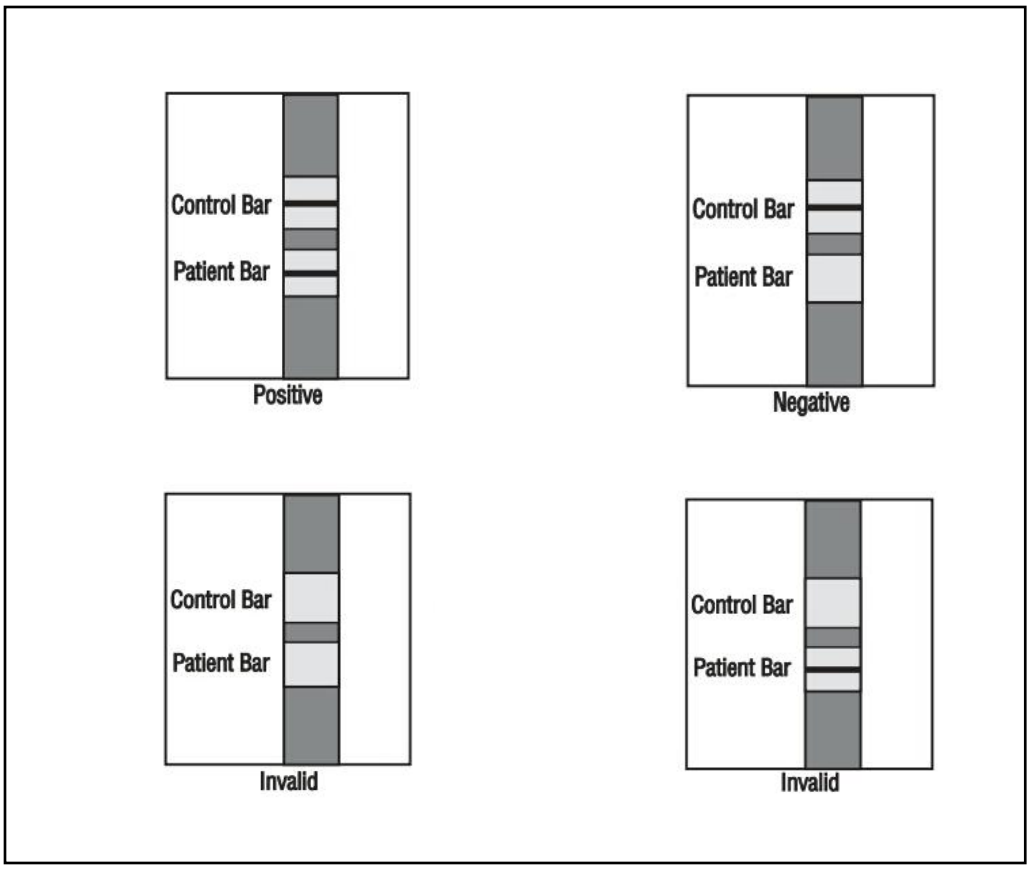


Figure 4.3: Results interpretation in detection of Treponema pallidum antibodies using an immunochromatographic test

4.6 Data entry and analysis

Data were entered and analysed using SPSS version 24. All blood donors who fulfilled the inclusion and exclusion criteria were studied for their sociodemographic characteristics, which includes age, gender, race, occupation, number of donation and donation site. All characteristics were reported in frequency and percentages.

The prevalence of overall TTI and each of the TTI were also expressed in frequency and percentages. Among these seropositive blood donors, the seroconvert blood donors were identified and reported in frequency and percentage out of total donations.

The identified risk factors for TTI, which include intravenous drug user, unsafe sexual practices, previous history of blood transfusion, family history were reported as frequency and percentage. The association of the identified risk factors and each of the TTI were checked for significance using Fisher's exact test. *P*-value of <0.05 were considered as significant.

The association between seropositivity and sociodemographic characteristics (age, gender, marital status, occupation, number of donation, and donation site) were checked for significance by simple and multiple logistic regression. The variables of occupation were divided into few categories, which includes student, uniform body, government sector, private sector, self-employed and unemployed. The uniform body were separated from the government sector in view of higher number of seropositive donors found within this occupational group. From simple logistic regression analysis, variables with *p*-value

of <0.25 were included in multiple logistic regression. *P*-value of <0.05 in multiple logistic regression were considered as significant, and results were reported in adjusted odds ratio with 95% confidence interval.

4.7 Ethical consideration

Ethical clearance was obtained from the Human Resource Ethics Committee of USM (JEPeM) (Appendix B) and Medical Research & Ethics Committee (MREC), MOH Malaysia (Appendix C). Because of limitation of the study (retrospective review of blood donors' record), informed consent was not gained from the study individuals. The gathered information of individuals were anonymized and de-identified prior to analysis. The researchers had no conflict of interest related to this study.

Chapter 5

Results

5.0 RESULTS

5.1 Sociodemographic characteristics of blood donors

There was a total of 94 989 donations in 2011 until 2017 which fit in the inclusion and exclusion criteria. The demographic characteristic data of all the donations were summarized in Table 5.1. Most of the donations were from male (66.1%), Malay (91.6%), and repeat donors (61.3%). It was also noted that students contributed more than half of the donations (53.4%). The donations at mobiles showed a higher proportion (84.7%) compared to donation at the centre.

Table 5.1: Sociodemographic characteristics of blood donations in HSNZ from 2011 to 2017 (n=94 989)

Variable		Total, n (%)
Age, *mean (SD)*		*26.90 (3.78)*
Gender		
	Male	62 746 (66.1)
	Female	32 243 (33.9)
Race		
	Malay	88 133 (92.8)
	Chinese	4 724 (4.9)
	Indian	983 (1.0)
	Others	1 149 (1.2)
Occupation		
	Student	50 746 (53.4)
	Non-student	44 243 (46.6)
Number of donation		
	First time	36 808 (38.7)
	Repeat	58 181 (61.3)
Donation site		
	Centre	14 553 (15.3)
	Mobile	80 436 (84.7)

5.2 The prevalence of seropositive and seroconvert blood donors

The overall prevalence of seropositive and seroconvert blood donors from 2011 to 2017 were 0.35% and 0.014% respectively. Seropositive donors are those who were found to be positive for any of the four TTI tested, while seroconvert donors were those who were found to be serologically positive during their current donations but were serologically negative during previous donations. These seroconvert donors were also included in the total number of seropositive donors.

Table 5.2 showed that the year 2011 recorded the highest prevalence of seropositivity (0.44%) followed by 2016 (0.42%) and 2015 (0.38%). On the other hand, for seroconversion, the highest prevalence was recorded in the year 2014 (0.031%) followed by 2011 (0.023%). There was no seroconversion recorded in the year 2015.

Table 5.2: The prevalence of seropositive and seroconvert blood donors by year of donation

Year	Total donations	Seropositive donors, n (%)	Seroconvert donors, n (%)
2011	13 215	58 (0.44)	3 (0.023)
2012	13 333	48 (0.36)	1 (0.008)
2013	12 694	40 (0.32)	2 (0.016)
2014	12 842	34 (0.26)	4 (0.031)
2015	14 094	53 (0.38)	0 (0.000)
2016	14 217	60 (0.42)	2 (0.014)
2017	14 594	37 (0.25)	1 (0.007)
Total, n (%)	**94 989**	**330 (0.35)**	**13 (0.014)**
Mean (per year)	**13 569.9**	**47.1**	**1.9**

Among the four TTI studied, HBV showed the highest prevalence (0.17%), followed by HCV (0.11%), syphilis (0.04%), and HIV (0.02%) as shown in Figure 5.1.

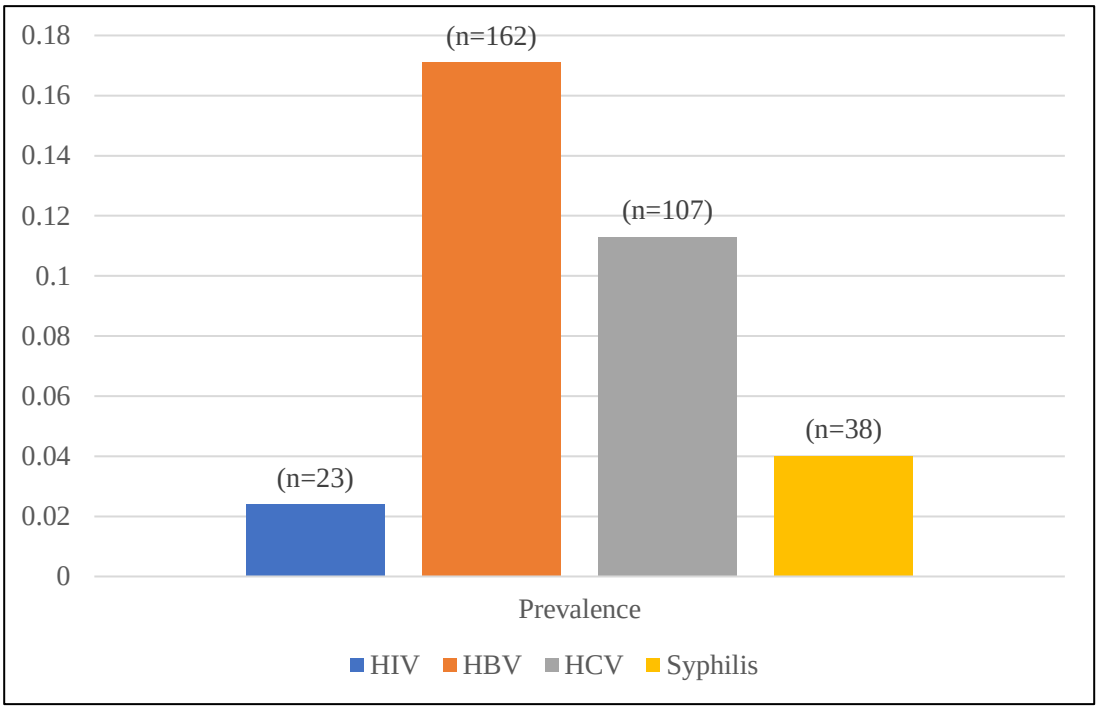


Figure 5.1: The prevalence of seropositive blood donors of HIV, HBV, HCV, and syphilis (n=330)

Out of the total seroconvert cases (n=13), the highest seroconversion was seen with HIV infection (38%), followed by HCV (31%), HBV (23%) and syphilis (8%) (Figure 5.2).

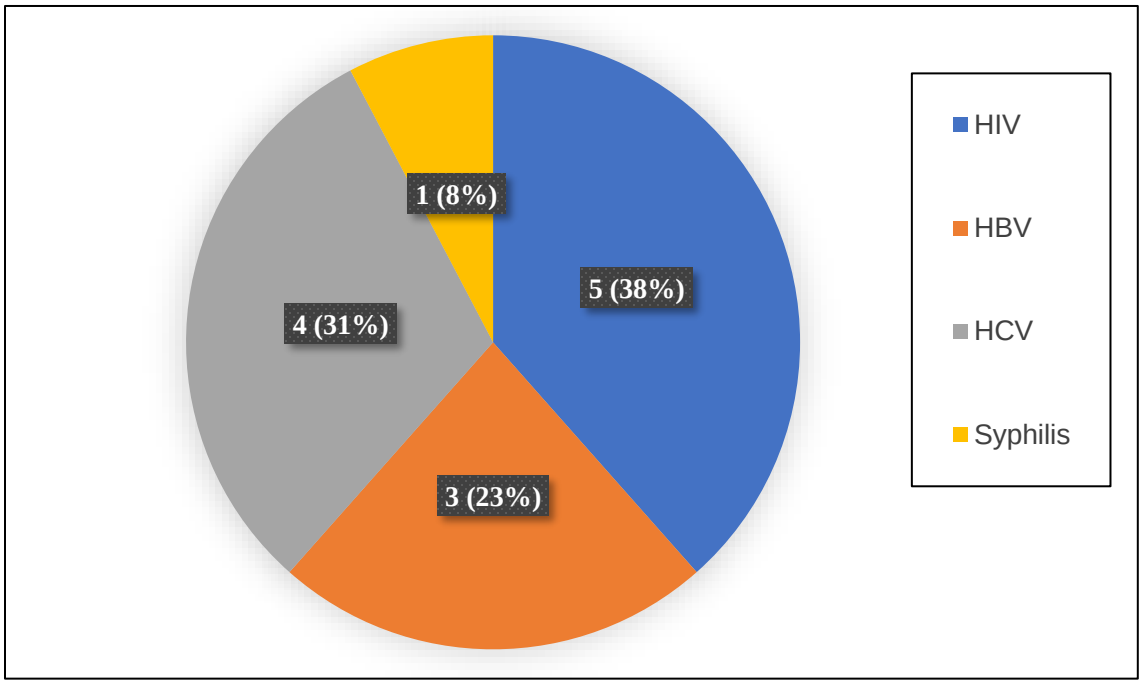
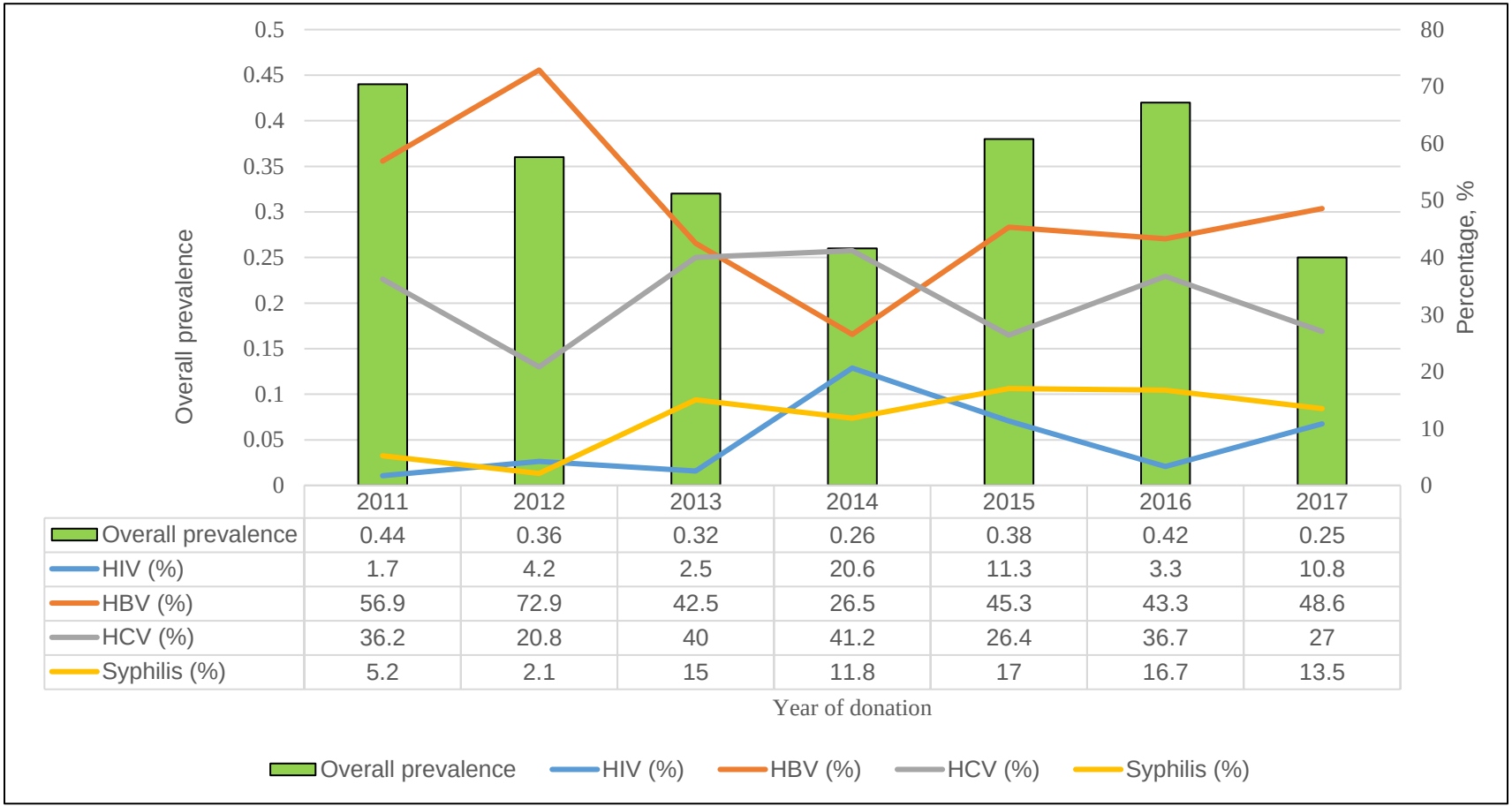


Figure 5.2: The proportion of seroconvert blood donors of HIV, HBV, HCV, and syphilis (n=13)

Overall, there was a decreasing trend of prevalence from the year 2011 until 2014, before it increased in 2015 until 2016, and reduced again in 2017. The pattern of HBV and HCV seropositivities showed almost similar trends to the overall prevalence's pattern, as these two infections contributed the most to the overall prevalence. The other two infections showed fairly static low prevalence from 2011 to 2017 (Figure 5.3).



	2011	2012	2013	2014	2015	2016	2017
Overall prevalence	0.44	0.36	0.32	0.26	0.38	0.42	0.25
HIV (%)	1.7	4.2	2.5	20.6	11.3	3.3	10.8
HBV (%)	56.9	72.9	42.5	26.5	45.3	43.3	48.6
HCV (%)	36.2	20.8	40	41.2	26.4	36.7	27
Syphilis (%)	5.2	2.1	15	11.8	17	16.7	13.5

Figure 5.3: The trends of seropositive blood donors of HIV, HBV, HCV and syphilis, comparing with the overall prevalence of seropositivity

5.3 The risk factors of seropositive blood donors

There was a total of four main risk factors of seropositivity identified in this study, which were intravenous drug user (IVDU), unsafe sexual practices, previous history of blood donations, and having family history of specific TTI. The majority of the identified risk factors among the seropositive blood donors were the unsafe sexual practices (51.7%), with majority of them having multiple sexual partners (74.2%), followed by men who have sex with men (MSM) (16.1%) and having sexual partner who had high risk behaviour (9.7%). All the seropositive blood donors of HIV and syphilis infections had unsafe sexual practices as the only identified risk factors. On the other hand, for donors with HBV infection, having family history of this infection were the highest risk factor. The IVDU showed to be the risk factor only for HCV infection. From the Fisher's exact test, it was shown that there were significant association between the risk factors and each of the TTIs (p <0.05) (Table 5.3).

Table 5.3: The risk factors identified among the seropositive blood donors

Risk factors	HIV n (%)	HBV n (%)	HCV n (%)	Syphilis n (%)	TOTAL n (%)
IVDU	0 (0.0)	0 (0.0)	5 (29.4)	0 (0.0)	**5 (8.3)**
Unsafe sexual practices (total):	5 (100.0)	9 (30.0)	9 (52.9)	8 (100.0)	**31 (51.7)**
Multiple sexual partners	1 (20.0)	7 (77.8)	8 (88.9)	7 (87.5)	23 (74.2)
MSM	4 (80.0)	0 (0.0)	0 (0.0)	1 (12.5)	5 (16.1)
Sexual partner with high risk behaviour	0 (0.0)	2 (22.2)	1 (11.1)	0 (0.0)	3 (9.7)
Previous blood transfusion	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	**1 (1.7)**
Family history	0 (0.0)	20 (66.7)	3 (17.7)	0 (0.0)	**23 (38.3)**
Total, n (%)	**5 (8.3)**	**30 (50.0)**	**17 (28.3)**	**8 (13.3)**	**60 (100)**
****p*-value**	**<0.001***	**<0.001***	**0.002***	**0.038***	

**p*-value <0.05; **Fisher's exact test; IVDU= intravenous drug user; MSM= men who have sex with men

5.4 The sociodemographic characteristics of cases and controls

The seropositive blood donors were predominantly males (85.4%), Malay donors (92.3%) with majority of the collection from first time donors (97.2%) and from mobiles (99.2%). The mean age of these seropositive donors was 31.3-year-old with students constituted 32.1% of the total seropositive donors. The proportion of married and unmarried donors were almost equal (Table 5.4).

The sociodemographic characteristics of the control group (n=240) showed almost similar distribution to the overall blood donors' characteristics, with mean age of 28.2-year-old. There were majority of male (52.1%) and Malay (95.4%) donors with students constituted the highest percentage (38.3%) in the occupation categories. Collection from mobiles also showed higher percentage (85.4%) compared to donation at the centre. In contrast to the case group, the control group showed majority of repeat donors (72.9%) instead of first-time donors. The unmarried donors also constituted more than half of the donors in the control group (61.3%) (Table 5.4).

Table 5.4: Sociodemographic characteristics of seropositive (case) and seronegative (control) blood donors (n=486)

Variables	Case, n=246 n (%)	Control, n=240 n (%)
Age		
Mean (SD)	*31.3 (10.77)*	*28.2 (8.90)*
17-29	121 (49.2)	146 (60.8)
30-49	105 (42.7)	87 (36.3)
50-65	20 (8.1)	7 (2.9)
Gender		
Male	210 (85.4)	125 (52.1)
Female	36 (14.6)	115 (47.9)
Race		
Malay	227 (92.3)	229 (95.4)
Chinese	6 (2.4)	6 (2.5)
Indian	1 (0.4)	0 (0.0)
Others	12 (4.9)	5 (2.1)
Marital status		
Married	113 (45.9)	93 (38.8)
Unmarried	133 (54.1)	147 (61.3)
Occupation		
Student	79 (32.1)	92 (38.3)
Government	36 (14.6)	59 (24.6)
Private sector	43 (17.5)	45 (18.8)
Uniform body	38 (15.4)	5 (2.1)
Self-employed	42 (17.1)	24 (10.0)
Unemployed	8 (3.3)	15 (6.3)
Number of donation		
First-time donor	239 (97.2)	65 (27.1)
Repeat donor	7 (2.8)	175 (72.9)
Site of donation		
Centre	2 (0.8)	35 (14.6)
Mobiles	244 (99.2)	205 (85.4)

5.5 The association of sociodemographic characteristics with seropositivity

Results from simple logistic regression (SLR) as shown in Table 5.5 showed that age, gender, occupation, number of donations, and donation site had a statistically significant association with seropositivity ($p<0.05$). The age group of 50-65-year-old had 3.4 times higher odds of being seropositive compared to the 17-29-year-old age group ($p=0.007$), while males had 5.3 times higher odds of being seropositive compared to females ($p<0.001$). In the occupation variables, working in uniform body and self-employed showed 8.8 times and 2 times higher odds respectively to be seropositive when compared to students ($p<0.001$ and $p=0.017$ respectively). The first-time blood donors were significantly had higher odds compared to repeat donors with *p*-value of less than 0.001. Donations from mobiles had 20 times higher odds of being seropositive compared to donations at the centre ($p<0.001$). All variables were included in the multiple logistic regression analysis ($p<0.25$).

Table 5.5: The association between sociodemographic characteristics and seropositivity by SLR (n=486)

Variables		Crude b	Crude OR (95% CI)	Wald statistics	*p*-value
Age (years)					
	17-29		1		
	30-49	0.376	1.456 (1.003, 2.114)	3.910	0.048*
	50-65	1.238	3.447 (1.410, 8.427)	7.365	0.007*
Gender					
	Female		1		
	Male	1.680	5.367 (3.474, 8.290)	57.339	<0.001*
Race					
	Malay		1		
	Non-Malay	0.497	1.644 (0.759, 3.557)	1.590	0.207**
Marital status					
	Unmarried		1		
	Married	0.295	1.343 (0.936, 1.927)	2.563	0.109**

Table 5.5. Continued

Variables		Crude b	Crude OR (95% CI)	Wald statistics	*p*-value
Occupation					
	Student		1		
	Uniform body	2.180	8.851 (3.327,23.574)	19.030	<0.001*
	Government	-0.342	0.711 (0.426, 1.186)	1.710	0.191*
	Private sector	0.107	1.113 (0.665, 1.862)	0.166	0.684
	Self-employed	0.712	2.038 (1.136, 3.657)	5.695	0.017*
	Unemployed	-0.476	0.621 (0.250, 1.542)	1.054	0.305
Number of donation					
	Repeat		1		
	First	4.521	91.923 (41.152, 205.333)	121.559	<0.001*
Donation site					
	Centre		1		
	Mobiles	3.036	20.829 (4.950, 87.651)	17.151	<0.001*

*p-value < 0.05; **p-value < 0.25; SLR=single logistic regression

From the multiple logistic regression (MLR) analysis, both the forward and backward methods gave the same decision for the results, where gender, occupation, number of donation, and donation site showed significant associations with seropositivity (p<0.05). Males were shown to have 5.8 times higher odds to be seropositive compared to females when adjusted for other variables (p<0.001). Those blood donors working in uniform body, at private sector, self-employed, and unemployed have 19, 2.9, 10, and 8 times higher odds respectively to be seropositive when compared to students (p=0.001, 0.017, 0.001, and 0.036 respectively). The first-time blood donors also showed a significantly higher odds to be seropositive when compared to repeat donors (p<0.001). In addition, blood donations from mobiles showed 10 times higher odds of being seropositive when compared to donations at the centre (p= 0.017) (Table 5.6).

Table 5.6: The association between sociodemographic characteristics and seropositivity by MLR (n=486)

Variables		Adjusted b	Adjusted OR (95% CI)	Wald statistics	*p*-value
Gender					
	Female		1		
	Male	1.771	5.879 (3.104, 11.134)	29.551	<0.001*
Occupation					
	Student		1		
	Uniform body	2.977	19.638 (3.500, 110.117)	11.450	0.001*
	Government	0.681	1.977 (0.825, 4.736)	2.336	0.126
	Private sector	1.075	2.930 (1.211, 7.092)	5.684	0.017*
	Self-employed	2.362	10.608 (2.074, 41.617)	11.467	0.001*
	Unemployed	2.116	8.297 (1.148, 59.983)	4.396	0.036*
Number of donation					
	Repeat		1		
	First	5.382	217.429 (75.162, 628.978)	98.612	<0.001*
Donation site					
	Centre		1		
	Mobile	2.368	10.674 (1.535, 74.231)	5.726	0.017*

*p-value<0.05; MLR multiple logistic regression; The model reasonably fit well. Model assumptions were met. There were no interaction and multicollinearity problem

Chapter 6

Discussion

6.0 DISCUSSION

6.1 Sociodemographic characteristics of blood donors

The sociodemographic characteristics of the overall blood donors in Terengganu showed that male donors constituted more percentages compared to females. Generally, this was in concordance with the Malaysian gender distribution, in which it recorded the sex ratio for Citizens was 103 males per 100 females in 2010 to 2014 and 102 males per 100 females in 2015 to 2019. The gender distribution in Terengganu also showed a slight male predominance (Department of Statistics Malaysia, 2018). This gender predilection had been also reported in a study done in Perlis, where males were reported to have more intention to donate blood, which might be due to their characteristics of being more responsible and courageous compared to females (Hamid *et al.*, 2013). Apart from that, it was also known that females had more factors that can prevent them from donating blood. One of the main factors was the higher prevalence of iron deficiency anemia among females (Agnihotri, 2010; Bahadur *et al.*, 2011; Milman, 2015; Awaluddin *et al.*, 2017). In developing countries, it was also noted that women usually did not come forward for blood donation due to many socio-cultural inhibitions, ignorance and fear for donating blood. This gender inequality could also be due to physiological changes in females that could make them ineligible to donate. These include monthly menstrual flow, pregnancy and lactation (Pandit *et al.*, 2015).

The ethnicity distribution for the overall blood donors reflected the general population of Terengganu, in which Malays constituted the majority of the population, followed by Chinese, Indian and other races (Department of Statistics Malaysia, 2018). Students

constituted more than half of the overall blood donors. This might be due to the fact that, mobiles for blood donation were frequently being set-up in the educational institutions (e.g. universities, colleges and secondary schools), as there were larger number of potential blood donors in these places. This was also one of the strategies for the blood banking service to introduce blood donation among students, which aimed at getting them to be regular blood donors in the future (Hurst *et al.*, 2007).

The results also showed that majority of the blood donors were the repeated blood donors compared to first time donors. This was in concordance with the study done previously in HSNZ (Ling *et al.*, 2018). Repeat blood donors were also the majority blood donors found in other studies worldwide (Van der Bij *et al.*, 2006; Unnikrishnan *et al.*, 2011; Carneiro-Proietti *et al.*, 2010). The intention to donate blood was reported to be associated with the individuals' knowledge and motivation towards blood donation (Mauka *et al.*, 2015). Another recent study done in HSNZ reported that majority of participants in their study had good knowledge and attitude towards blood donation (Noh *et al.,* 2019). Those who already had experience of donating blood, were most likely to get more knowledge and information regarding the benefits and importance of blood donation. With the addition of good experience on previous donations, these blood donors were likely to donate blood again in the future and became repeat or even regular donors (Misje *et al.*, 2005).

It was also noted from this study that more than 80% of the donations were from mobiles compared to donations at the centre. This finding was also reported by other studies elsewhere (Carey *et al.*, 2012; Morand *et al.*, 2016). Mobile blood donations had been

set up all over the state throughout the years, as one of the strategies to increase blood collection. The mobile blood donations were usually arranged with a sponsoring organization such as schools, universities, non-governmental organizations, religious groups or military installations. These mobiles enable donors to donate blood near their homes or at their workplaces, instead of coming to the hospital for blood donation. In general, blood donation centres were less convenient for donors in term of the need for additional travel and time. This was one of the possible reasons for donor preferences towards donation at mobiles (Nguyen *et al.*, 2008).

6.2 The prevalence of seropositive blood donors

This study reported a low overall prevalence of seropositive blood donors in Terengganu from the year 2011 to 2017. The prevalence for each of the TTI was also low and was within the ranges specified by the WHO for upper middle-income countries (WHO, 2017). However, data on the prevalence of TTI among Malaysian blood donors was lacking up to this point of time except for few, small-centred studies which concentrated on one specific infection, rather than overall seroprevalence. The prevalence of HBV infection was slightly lower compared to the prevalence reported by a study done among blood donors in Kelantan (1.1%) (Yousuf *et al.*, 2007). The prevalence of HCV infection was similar to a reported prevalence of a study done in a teaching hospital in northeastern Malaysia (0.14%) (Haslina *et al.*, 2012). However, earlier study done in Kuala Lumpur reported a slightly higher HCV prevalence (1.49%) among blood donors (Duraisamy *et al.*, 1993).

Studies done worldwide reported a wide range of TTI prevalence among blood donors. A single centre study conducted in Turkey reported the HIV, HBV, HCV and syphilis seropositivities of 0.003%, 1.66%, 0.05% and 0.10% respectively, with overall prevalence of 1.8% which were almost similar to our results (Yildiz *et al.*, 2015). Other studies done in Shiyan, Central China and Nigeria also reported only slightly higher overall prevalence compared to our study, which were 1.35% and 0.9% respectively (Nwokeukwu *et al*., 2014; Yang *et al*., 2016). A study done in Cameroon involving both volunteer and replacement donors reported a much higher overall TTI prevalence of 21.2%. The seroprevalence rates of HIV, HBV, HCV, and syphilis were 4.1%, 10.1%, 4.8%, and 5.7%, respectively (Noubiap *et al.*, 2013). Other studies done in Ethiopia and Kyrgyzstan, also reported much higher prevalence compared to our results (Abate &

Wolde, 2016; Karabaev *et al.*, 2015). In India, the prevalence reported varied between different states; where up to 4.36% seroprevalence reported in Delhi, while lower prevalence of 1.4% was reported in Karnataka (Ahmed *et al*., 2015; Rawat *et al*., 2017). The difference in the prevalence of seropositive blood donors reported between countries might be dependent on the seroprevalence among the general populations. Apart from that, the difference also contributed by the donor type and donor selection criteria applied by the respective blood collection services. The places that allowed donation from other than volunteer donors tend to have higher prevalence of seropositive donors (Jain *et al*., 2013; Shah *et al.*, 2013).

Despite a moderately high prevalence of HIV, HBV, HCV and syphilis infections among general population of Terengganu, the lower prevalence of seropositive blood donors showed that the measures such as self-deferral and strict donor selection had played an important role in preventing the seropositive individuals from donating blood. Few studies reported that high risk behaviours were one of the main reasons for deferral from blood donations (Vimal *et al*., 2016; Hatami *et al.,* 2018).

6.3 The prevalence of seroconvert blood donors

This study also reported a low overall prevalence of seroconvert blood donors. The result was almost similar with the result reported by the NBC, Kuala Lumpur in 2016 which showed 0.064% seroconversion rate among their repeated blood donors (Nafishah *et al*., 2014). Other studies worldwide also reported a low prevalence of seropositivity among repeat blood donors (Mavenyengwa *et al.*, 2014; Song *et al.*, 2014; PourfathollahPhD, 2014).

This finding of low prevalence was possibly due to the high sensitivity of the serological methods used for donor screening. In this group of donors, there were two possibilities of how the conversion of the serologic testing occurred. Firstly, they were in the window period during the first donation, thus were tested negative by serology. Although this constituted only a small percentage out of the total donations, it could cause serious effects to the patients. Therefore, more sensitive techniques for screening such as NAT should be implemented to complement the serological tests. The second possibility was that these repeat donors got a new infection in between the donations by any means of transmission. These include the involvement in unsafe sexual practices or other high risk behaviours. However, a study reported that the risk of such infection occurring was considerably less compared to the prevalence of infection present in first time donors (Allain, 2011).

6.4 The trend of seropositive blood donors

The trend of the overall seropositivity showed initial decreasing pattern from 2011 until 2014, before showing an increment in 2015 to 2016 and decreased again in the year 2017. When comparing with the trend of the four studied TTI, it was noted that HBV seropositivity showed almost similar trend with the overall seropositivity, as it contributed the most percentages to the overall seropositivity. The trends of both HBV and HCV infections were actually very similar to the trends of the seropositivity among general population of Terengganu, from the year 2011 until 2017. This were also true for both the HIV and syphilis seropositivity which showed a static low trend over the same period of time, which was in parallel with the prevalence among general population in this state (Health indicator, MOH 2012-2018). In addition, the Country Progress Report on HIV/AIDS 2018, MOH also reported that the new HIV infections had remained static between 2010 and 2017 at average of 3,400 cases per year (MOH, 2018).

Other than the agreement with the trends of the prevalence among general population, there might be other factors that contributed to these trends. One of the possible reasons was the change of the administrative and staffing in the blood banking service. Different leader would have conducted different donor recruitment programs. Thus, might give different detection rate of seropositive donors. These was also true for the donor selection during donor interview, where different medical officers had different ways of interviewing with different interpretation towards a prospective donor. The more experienced ones might have higher possibilities to detect potential seropositive donors, thus deferral from blood donation was made. This showed that an effective donor counseling is crucial (Kulkarni and Kulkarni, 2014).

The trend of seropositive blood donors reported in other countries were varied. A study conducted in China on four different blood centres showed that the prevalence of HBV and HCV demonstrated a decline trend in all blood centres. However, HIV and syphilis showed variable trends in all four centres. The decline of the HBV and HBC was thought to be possibly due to the increment in the proportion of the population already been diagnosed with both viruses. Thus, reducing the possibility of these diagnosed people from donating blood. Other than that, the decline also might be due to the improvement in the effectiveness of education and screening processes (Li *et al.*, 2012). Another study in north India reported a significantly decreasing trends of HIV, HBV and syphilis among blood donors throughout a nine-year period. Only the HCV showed an insignificant increased in trend (Makroo *et al.*, 2015). Apart from that, a study also reported that all transfusion-transmissible infections declined significantly with remarkable decline in HIV, within eleven years. These decreases were in consonance with reported decline in the seroprevalence among general population in their country (Okoroiwu *et al.*, 2018).

6.5 The risk factors of seropositive blood donors

Out of the total seropositive blood donors identified in this study (n=330), only 114 donors' counseling record were available in our blood bank registry. The remaining seropositive blood donors were actually seen and counselled at other centres due to logistic reason. As most of the blood donations in HSNZ were from mobiles, which took place in all eight districts of Terengganu state, these seropositive blood donors were seen in their respective district hospitals' blood banking services. Some of these seropositive blood donors came from other parts of Malaysia, especially students in the universities or colleges and workers who did not permanently stay in this state. These donors usually requested to be seen in their nearest blood banking services at other states. Out of these 114 seropositive blood donors, 54 did not have their risk factors documented in the counselling record, thus were excluded for the study on risk factors. The current practice of seropositive donor counselling did not involve one seropositive donor being counseled by the same health care worker at each visit. This resulted in multiple medical personnel came in contact with the same seropositive donor. Subsequently, this might cause the donor to be anxious about the confidentiality issue, especially in revealing the risk factors.

The identified risk factors showed significant association with all the four studied TTI ($p<0.05$). The main risk factor identified was the unsafe sexual practices, with having multiple sexual partners was the main risk factor, followed by MSM. The category of having multiple sexual partners included those who had sexual contact with commercial sex workers or paying or being paid for sex. It was well-described in previous studies that these groups of individuals were at higher risk of transmitting the TTI (Musto *et al*, 2008). Schuelter-Trevisol *et al*. (2013) also concluded from their study, that sex workers

had high HIV infection rates, coinfection with viral hepatitis and syphilis. A study among blood donors conducted in India revealed that 20.3% seropositive donors had significant history of high risk behaviours (Sachdev *et al*., 2015). A case control, multi-blood centre study conducted in China, showed significant differences in risk factors for TTI between HIV-positive and HIV-negative blood donors. The HIV-positive donors were more likely to have the following high-risk behaviors: having two or more sexual partners, paying or receiving money for sex, being MSM, having been diagnosed with a sexually transmitted disease and having a tattoo (Wang *et al.*, 2013). Another case control study among blood donors in United State of America reported that history of having sex with an HIV-positive person was the strongest associated factor with HIV infection followed by MSM (Custer *et al.*, 2015).

This study showed that IVDU was the risk factor for HCV infection, but not for the other three infections. HCV transmission was known to have a high association with injecting drug use (de Paula Cavalheiro *et al.*, 2010; Chao *et al*., 2011; Nguyen *et al.*, 2010). The finding from this study was in parallel with other studies done elsewhere (Luksamijarulkul *et al.*, 2004).

Another main risk factor identified in this study was having family history of the infections, specifically the hepatitis viruses. This confers transmission of these viruses either through close contact or being born from infected mother. Sachdev *et al*. (2015) reported a significant association between history of jaundice in the donor, family or close contacts with HBV infection among blood donors in India. Another study also reported a significant

association of having family history of hepatitis with HBV and HCV infections among blood donors (Custer *et al.*, 2015).

Previous history of blood transfusion showed to be the risk factor in only one seropositive donor in this study, which was having HBV infection. Previous study reported that history of blood transfusion was present in seropositive donors of all TTI but was shown to be significant only for HCV infection (Custer *et al.*, 2015). This study showed that previous history of blood transfusion was not the main risk factor for TTI among blood donors. As described earlier, there was a list of criteria to be fulfilled before a person was allowed to donate. In general, blood donors were healthy individuals, thus they usually do not have history of blood transfusion. This is with exception if they involved in accident or trauma which required blood transfusion (Atsma *et al.*, 2011).

6.6 The association of sociodemographic characteristics and seropositivity

From this study, it was found that gender, occupation, number of donation and donation site had significant associations with seropositivity. Male blood donors were found to have significantly higher odds to be seropositive compared to female blood donors. This was also reported by previous studies done elsewhere (Karabaev *et al.*, 2017; Pandit *et al.*, 2015). However, these results were contradicting with a study done in China in which they reported females were the ones who had significant increased risk of being seropositive blood donors compared to males (Yang et *al.*, 2016).

The gender predilection shown in our study was probably contributed to the fact that males usually had higher risk of getting involved in the high risk behaviours such as unsafe sexual practices and intravenous drug use (MacArthur *et al.*, 2012). On the other hand, females were reported to have some protection provided by estrogens, specifically against HBV infection. Studies have shown that estrogens reduced the HBV proliferation as well as the risk of chronicity (Tong, 2012).

In our study, working in the uniform bodies such as policemen, firemen and soldiers showed the highest risk of being seropositive blood donors, when compared to students. Other occupational groups also showed to be significantly associated with seropositivity, except for working as government servants. Results from this study were similar to a study which was done in a teaching hospital in northwest Ethiopia (Tessema *et al.*, 2010). Another study conducted in Tehran also reported a higher prevalence of seropositive donors among those in non-governmental occupational groups (PourfathollahPhD, 2014). In contrast, a study in Nigeria showed totally different results from our study. They

found that students showed higher prevalence rates of TTI, when compared to other occupational groups (Okocha *et al*., 2015).

The results from our study were possibly due to the fact that males predominated in the uniform bodies (Power, 2017). Apart from that, Birku *et al.* (2015) also reported an intermediate prevalence (4.2%) of HBV infection among military personnel in their study. There were few possible reasons for this finding. In most cases, military people lived in military camps which might predispose them to HBV and HCV transmission through some common routes. The risk of sharing utensils such as razors and toothbrushes was common among people living in groups that could facilitate transmission of the viruses (Lock *et al.*, 2006). Moreover, they usually traveled from place to place and stayed apart from their family in longer duration. This might force them to have multiple sexual partners that could expose them for different sexually transmitted infections including HBV and HCV (Terrault *et al.*, 2013).

On the other hand, students were less likely to be seropositive probably due to their dependency and continuous supervision from the parents, guardians and teachers (Nawaz, 2011).

When comparing the number of donation, the first time blood donors had significantly higher odds of being seropositive, compared to those who donated repeatedly. This result was in agreement with other studies done worldwide (Bisseye *et al.*, 2014; PourfathollahPhD, 2014; Tessema *et al.*, 2010). The significant increase of seropositivity among first time blood donors was most likely due to the fact that first time blood donors

were those that most probably did not know their seropositivity status. In few occasions, there were also donors who had high risk behaviours, intentionally donated blood just to check their infection status. In any circumstances, any donor who was found to be seropositive, would be permanently deferred from further blood donation. It was also thought that regular donors usually have a profile of a low risk of infection because they had been selected many times. A study also reported that recent and active blood donors exhibited a healthier lifestyle compared to the general population (Atsma *et al.*, 2011).

The donation at mobiles showed a significant increased odds of being seropositive compared to donations at the centre. This finding was in parallel with previous studies conducted in Iran (PourfathollahPhD, 2014; MehdiSajjadi, 2017; Paridar *et al.*, 2018). Donations at mobile setting usually were done in order to increase the number of potential donors. In mobile setting especially in an open area such as in shopping malls or in open halls, there were lack of privacy during donor screening and counseling. This resulted in unrevealing of the risk factors, if any. The self-deferral strategy would also less likely to be employed by the prospective donors as they would enable themselves to donate. This was to avoid curiosity from colleagues or friends when they chose to self-defer. In addition, there was possibility of less stringent criteria applied for donor selection in mobile settings either due to pressure from organizers or the enthusiastic donors.

Older age groups relatively showed higher risk of being seropositive although this was not statistically significant when adjusted to other variables. This age group distribution of seropositive blood donors that was seen in our study was consistent with the age distribution of seropositivity among general population. The seroprevalence were

successfully reduced for HBV infection because of the infancy immunization program which was introduced in 1989. However, the disease burden remained high for some time as the infected people were getting older (Raihan R, 2016). This finding was consistent with a study done in Ethiopia where they reported a relatively higher prevalence rate observed among older age blood donors (Tafesse *et al.*, 2017). A systematic review of two hundred and sixty-five studies in China also reported that the prevalence of HCV infection among their blood donors was found to increase with age (Gao *et al.*, 2011). This finding was most probably due to the fact that students constituted most of the lower age group donors, which resulted in lower risk of seropositivity as discussed earlier. Apart from that, it was reported that people in older age group had higher risk of getting involved in high risk behaviours (Cheah *et al.*, 2019).

There was higher prevalence of seropositive blood donors seen in Malays (92.3%) and unmarried (54.1%) individuals. However, both of these variables were not statistically significant. A population study in Iran reported a higher prevalence of HBV infections among unmarried individuals (Amini *et al.*, 1993). Another study done by Arshad *et al.* (2016) showed that unmarried donors were more likely to be positive for HBV and syphilis. However, a study in Tehran reported a higher prevalence of infectious markers in married donors compared to unmarried donors (PourfathollahPhD, 2014). The result of this study was most probably due to the fact that more unmarried people were having high risk behaviours. On the other hand, the married individuals were probably had families to take care of and responsible for, thus less likely to get involved in high risk behaviours (Vandepitte *et al.*, 2011).

6.7 Limitations of the study

There were several limitations encountered during the preparation and completion of this study.

1. Data on the overall blood donations and the seropositive blood donors were not complete, causing difficulty in data collection and analysis. Few demographic data such as marital status and occupations were not properly documented or entered in the online system. This resulted in difficulty in categorizing in specific groups and requiring further search on original hardcopy of donor questionnaire form.
2. More than half of the seropositive blood donors were actually being seen and counselled in other district hospitals all over Terengganu. Therefore, their data were not available in our center, thus further reduced the available data on the risk factors of seropositive donors.
3. Due to small number of seropositive blood donors for each of the TTI studied, hence the association was only reported for overall seropositive blood donors. The association study for each of the TTI was unable to be accomplished.

Chapter 7

Conclusion

7.0 CONCLUSION

In conclusion, there was a low prevalence of seropositive and seroconvert blood donors in this study. These reflects an effectiveness of donor selection procedure. However, the donor recruitment and selection process should be improved in order to further reduce the prevalence of TTI. Screening of blood donors using serological test do not totally eliminate the risk of having the infection in view of a variable length of window period in different TTI. Therefore, more sensitive screening method such as NAT would be very beneficial. Since the implementation of NAT in the NBC in 2007, the usage of this test has been expanded gradually to cover all states in Malaysia. Starting early 2019, NAT has become a complementary test for most of donations in Malaysia.

Considering the significant lower risk of being seropositive in females, they should be encouraged to come forward and donate blood. Actions need to be taken to tackle the fear of donating blood in females. The problem of iron deficiency anaemia among these group of potential blood donors should also be managed appropriately. Recruiting regular blood donors are also crucial to further reduce the prevalence of TTI among blood donors. Strategies that focus on retaining return donors and transforming first-time donors into repeat donors would be beneficial. The target should be on students, where the awareness and importance of blood donations should be stressed on in the school. They should be encouraged and groomed to be regular donors in the future. For mobiles setting, a proper set-up should be done, especially during donor counselling in order to maintain donors' privacy. The improvement in donor selection and screening is also crucial in order to reduce the number of seropositive donations.

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APPENDICES

APPENDIX A – Data collection form

Subject number:

Year of donatiion:

Age:

Seropositivity:

☐ HIV ☐ Hep B ☐ Hep C ☐ Syphilis

Gender : ☐ M ☐ F

Race : ☐ M ☐ C ☐ I ☐ Others:

Marital : ☐ Single ☐ Married ☐ Divorced/widowed

Occ : ☐ Student ☐ Gov. ☐ Private

☐ Uniform ☐ Self-emp ☐ Unemployed

No donate: ☐ First ☐ Repeat

Risk Factors:

( ) IVDU

( ) Multiple sexual partners

( ) MSM

( ) Sexual partner with high risk behavior

( ) Previous blood transfusion

( ) Family history

( ) Others:

( ) No risk factor elicited

APPENDIX B – Ethical approval (JEPeM USM)

UNIVERSITI SAINS MALAYSIA

JAWATANKUASA ETIKA PENYELIDIKAN MANUSIA

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

Universiti Sains Malaysia
Kampus Kesihatan,
16150 Kubang Kerian, Kelantan, Malaysia
T : (6)09-767 3000/2354/2362
F : (6)09-767 2351
E : jepem@usm.my
L : www.jepem.kk.usm.my
www.usm.my

5th July 2018

013-3580309

Dr. Adibah Daud
Department of Hematology
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/18020124
Protocol Title : The Prevalence of Reactive Blood Donors in Hospital Sultanah Nur Zahirah, Kuala Terengganu and Its Associated Risk Factors.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/18020124**, which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from **5th July 2018** until **4th July 2019.**

Study Site: Hospital Sultanah Nur Zahirah, Kuala Terengganu.

The following researchers also involve in this study:

1. Dr. Marini Ramli
2. Dr. Mohd Nazri Hassan
3. Dr. Azly Sumanty Ab Ghani

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the abovementioned documents, the following technical document was included in the review on which this approval was based:

1. Data Collection Sheet

Attached document is the list of members of JEPeM-USM present during the full board meeting reviewing your protocol.

While the study is in progress, we request you to submit to us the following documents:

1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2017: Continuing Review Application Form.** Subsequently this need to be done yearly as long as the research goes on.
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2017: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2017: Study Protocol Amendment Submission Form.**

CERTIFIED BY: National Pharmaceutical Regulatory Agency (NPRA) | Forum for Ethical Review Committees in Asia & Western Pacific Region

4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2017: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2017.**
6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2017: Final Report Form.**

Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

Jawatankuasa Etika Penyelidikan (Manusia), JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

"ENSURING A SUSTAINABLE TOMORROW"

Very truly yours,

PROF. DR. HANS AMIN VAN ROSTENBERGHE
Chairperson
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia

APPENDIX C – Ethical approval (MREC KKM)

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Tel.: 03-2287 4032/2282 0491/2282 9085
03-2282 9082/2282 1402/2282 1449
Faks: 03-2282 0015

Ruj.Kami : KKM.NIHSEC. P18-1773 (5)
Tarikh : 18 -September-2018

DR ADIBAH BT DAUD
HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU

YBhg. Dato' / Tuan / Puan,

SURAT KELULUSAN ETIKA: NMRR-18-1666-41106 (IIR)
THE PREVALENCE OF REACTIVE BLOOD DONORS IN HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU AND ITS ASSOCIATED RISK FACTORS.

Lokasi Kajian:

HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) tiada halangan, dari segi etika, ke atas pelaksanaan kajian tersebut. JEPP mengambil maklum bahawa kajian tersebut hanya melibatkan pengumpulan data melalui:

i. **Data sekunder**

3. Segala rekod dan data subjek adalah **SULIT** dan hanya digunakan untuk tujuan kajian ini dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi.

4. Kebenaran daripada Pegawai Kesihatan Daerah / Pengarah Hospital dan Ketua-Ketua Jabatan atau pegawai yang bertanggungjawab disetiap lokasi kajian di mana kajian akan dijalankan mesti diperolehi sebelum kajian dijalankan. YBhg. Dato' / Tuan / Puan perlu akur dan mematuhi keputusan tersebut. Sila rujuk kepada garis panduan Institut Kesihatan Negara mengenai penyelidikan di Institusi dan fasiliti Kementerian Kesihatan Malaysia (Pindaan 01/2015) serta lampiran *Appendix 5* untuk templet surat memohon kebenaran tersebut.

5. Adalah dimaklumkan bahawa kelulusan ini adalah sah sehingga 17 **-September-2019**. YBhg. Dato'/ Tuan/ Puan perlu menghantar dokumen-dokùmen seperti berikut selepas mendapat kelulusan etika. Borang-borang berkaitan boleh dimuat turun daripada laman web Jawatakuasa Etika & Penyelidikan Perubatan (JEPP) (http://www.nih.gov.my/mrec).

i. ***Continuing Review Form*** selewat-lewatnya dalam tempoh 1 bulan (30 hari) sebelum tamat tempoh kelulusan ini bagi memperbaharui kelulusan etika.

ii. ***Study Final Report*** pada penghujung kajian.

iii. Mendapat kelulusan etika sekiranya terdapat pindaan ke atas sebarang dokumen kajian / lokasi kajian / penyelidik.

6. Sila ambil maklum bahawa sebarang urusan surat-menyurat berkaitan dengan penyelidikan ini haruslah dinyatakan nombor rujukan surat ini untuk melicinkan urusan yang berkaitan.

Sekian terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menurut perintah,

(DR HJH SALINA ABDUL AZIZ)
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia
mrecsec@nih.gov.my
03-2282 9085

s.k.: HRRC Hospital Nur Zahirah

MAz/Approval2018/Mrecshare

APPENDIX D – Poster presentation at Malaysian Society of Haematology (MSH) Annual Scientific Meeting 2019

A PRELIMINARY REPORT ON HIV, HEPATITIS B, HEPATITIS C, AND SYPHILIS INFECTIONS AMONG BLOOD DONORS IN HOSPITAL SULTANAH NUR ZAHIRAH (HSNZ) KUALA TERENGGANU AND ITS ASSOCIATED RISK FACTORS

Adibah Daud[1], Marini Ramli[1], Mohd Nazri Hassan[1], Azly Sumanty Ab Ghani[2]

[1]Department of Haematology and Transfusion Unit, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan.
[2]Pathology Department, Hospital Sultanah Nur Zahirah, Kuala Terengganu.

INTRODUCTION

Blood transfusion is one of the measure used in modern medicine to manage patients, especially those who are anaemic or having significant blood loss. This measure is not without risk, with one of the concerned risk is **transfusion transmitted infection (TTI)**. Therefore, screening for the TTI is very important to make sure that blood products given to patient are at the safest level. In Malaysia, all blood donated were screened for Human Immunodeficiency Virus (HIV), Hepatitis B (Hep B), Hepatitis C (Hep C), and Syphilis.

OBJECTIVES

- To determine the prevalence of reactive donors of HIV, hepatitis B, hepatitis C, and syphilis in HSNZ.
- To determine the rate of seroconversion of TTI among blood donors in HSNZ
- To determine the associated risk factors and socio demographic characteristics of reactive blood donors in HSNZ.

MATERIALS AND METHOD

This is a retrospective study, involving record review of all blood donors in HSNZ from 2011 until 2017. The data of blood donors were extracted from E-delphyn online system. The data on reactive blood donors were extracted from the SUKUSA online system and donors' counseling records.

RESULTS

There was a total of **94,989 blood donations** in HSNZ from 2011-2017, with majority of donors were **Malays** (92.78%) and **males** (66.06%).

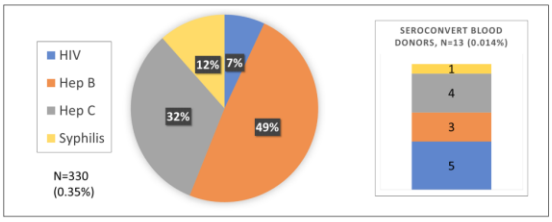

FIGURE 1. Seropositive and seroconvert blood donors (inlet) for HIV, Hep B, Hep C, and syphilis in HSNZ, 2011-2017.

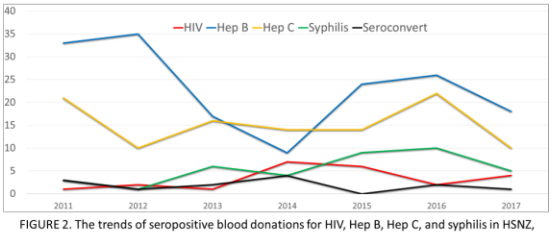

FIGURE 2. The trends of seropositive blood donations for HIV, Hep B, Hep C, and syphilis in HSNZ, 2011-2017

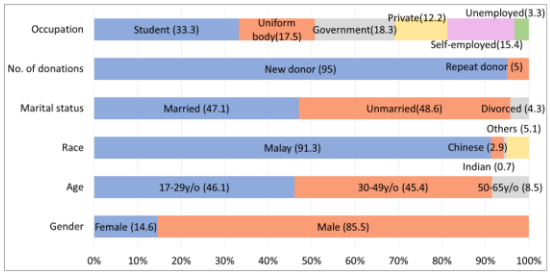

FIGURE 3. Socio-demographic data of seropositive blood donors in HSNZ, 2011-2017 (n=246)

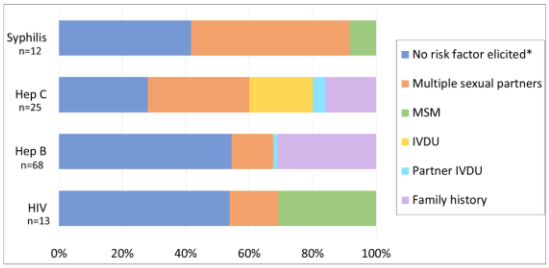

FIGURE 4. Associated risk factors of TTI among seropositive blood donors in HSNZ, 2011-2017
* Donors who denied high risk behaviour, previous history of blood transfusion, or any family history.

DISCUSSION

The prevalence of seropositive blood donors were low in HSNZ, when compared to other studies worldwide[1-3]. However, it is comparable to a study conducted in China[4]. The finding of low prevalence of seroconvert blood donors was almost the same as a study conducted in National Blood Centre (NBC) in 2010[5]. There was also reducing trend of seropositive blood donors observed. Most of the reactive blood donors were Malay male, in keeping with the fact that majority of our blood donors were Malay male. This gender predilection was also reported in few other studies[2,5] Students were also reported to be the highest contributor to the number of reactive blood donors[4]. Another study reported that most of the seropositive blood donors were the first time donors and at younger age group[3]. Men-sex-men (MSM) was the main risk factor for HIV, while multiple sexual partners was the main risk factor for both hep C and syphilis infections.

CONCLUSION

In conclusion, the prevalence of reactive blood donors in HSNZ is low and showing reducing trend, with hep B as the most frequent infection. The majority of these reactive blood donors were Malays, males, students, and first time donors. The most common associated risk factors were multiple sexual partners and MSM, other than family history in hep B infection.

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