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Prevalence and Trends of HBV, HCV, and HIV Serological and NAT Markers and Profiles in Saudi Blood Donors

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Abstract

Background: Epidemiologic studies on the prevalence of transfusion-transmitted infections (TTIs) in Saudi Arabia (SA) regions are limited. This study investigated the prevalence of HBV, HCV, and HIV using both serological and nucleic acid testing (NAT) methods to determine temporal and geographic trends among blood donors in Makkah. Our secondary objective was to realize the most suitable NAT format, without compromising sensitivity of NAT results by using individualized or mini-pool testing.

Methods: Serologic and NAT screening records of 22,963 blood donors from January 2011 to December 2014 were evaluated for HBsAg, Anti-HBc, Anti-HCV, Anti-HIV, HBV-DNA, HCV-RNA, and HIV-RNA. Prevalence rates were calculated for TTIs per hundred donations and additional analysis was conducted to examine donor profiles associated with positive serologic and NAT results. Known viral loads (<20 IU/ml for each HBV and HCV and <50 copies/ml HIV) diluted in negative plasma were evaluated by NAT screening.

Results: Overall serological prevalence of HBs-Ag, anti-HBc, anti-HCV, and anti-HIV were 0.7, 6.7, 0.44, and 0.07%, while molecular HBV-DNA, HCV-RNA, and HIV-RNA were 0.72, 0.05, and 0.03% respectively. There was a gradual decline in percentage of infected donor blood based on combined serological and/or NAT screening from 8.3% in 2011 to 6.8% in 2014 with an overall 7.4% (n=1,689) TTI-infected. Prevalence of HBV, HCV and HIV was unevenly distributed among different regions in SA. Analysis of donor serologic and molecular profiles revealed solitary anti-HBc- positive was the highest (6%) donor profile followed by anti-HBc-positive/HbsAg-positive/HBV-DNA positive donor profile at 0.6%, and solitary anti-HCV at 0.4%. Simulation of mini-pool NAT format by dilution of known viral loads at 1:6, resulted in 70% reduction in HBV detection, 50% for HCV, and 40% for HIV.

Conclusions: This is the first study to provide current data collectively comparing prevalence and trends of HBV, HCV, and HIV serologic and nucleic acid markers amongst Saudi blood donors. Makkah boasts one of the lowest TTIs prevalence in SA and to surrounding countries. The majority of seropositive and NAT-reactive blood donors are in a state of acute, chronic or resolved HBV infection. Individual donor NAT is the ideal methodology that should be applied in SA where diluted samples could compromise clinical sensitivity and blood safety.

Keywords: NAT; Sero-prevalence; Blood donor profile; Transfusion-transmitted infections; Saudi Arabia

Introduction

Annually, millions of people worldwide receive blood transfusions or blood-derived products. A single whole-blood donation can be transfused in up to three people, while blood-derived products are manufactured from pooled plasma of hundreds of donors. The available serological and molecular methods for testing the transfusion-transmitted infections (TTIs) are a routine global practice to guarantee the safety of blood and blood products supply. Hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV-1 & -2) are the three most important agents responsible for TTIs. To improve on the safety of the blood being donated, measures have been adopted by blood banks such as the use of stringent donor selection criteria, exclusion of those with clinical and theoretical risks of carrying infectious agents by the use of questionnaire, and encouragement and maintenance of voluntary pool of blood donors [1].

Detection of blood borne viruses by conventional serology tests relies on the production of viral specific antibodies, the level of virus antigens in blood and the sensitivity and specificity of serology method used. During this interval, also known as the serological window period, the virus is present in the blood of the infected individual and may be transmitted to the recipient of this infected blood even though the serological test is negative. To minimize the risk of TTI-associated serological window period, Nucleic Acid Testing (NAT) which is a highly-sensitive method for simultaneous detection of HBV, HCV, and HIV can be applied. Indeed, NAT has the advantage of shortening the serological window period of HBV to 10.34 days, HCV to 1.34 days, and HIV to 2.93 days [2]. NAT also adds the benefit of resolving false sero-reactive donations, which is very important for donor notification and counseling [3]. The need for NAT testing depends on the prevalence

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and incidence rate of infections in blood donor populations, and the evidence of benefit added when combined with serology tests. Given the impact that NAT can have in lowering the risk of TTIs, many countries employ NAT testing as a complement to traditional serology methods, performing both to fully optimize the safety of their blood supplies.

Common NAT platforms — fully integrated and automated, semi-automated, and modular automated types — are used with assays to conduct NAT screening in two ways: individual donor testing (IDT) and pooled testing. The number of samples used per each mini-pool may vary, which usually accommodates the requirements of the blood donation centers for overall sensitivity of the testing as well as the financial expenditures. IDT, generally considered the most sensitive method, is done on a sample from each unit of donated blood with no dilution of viral genetic materials required before testing. The viral titers during window periods are often low, and IDT can maintain a high level of sensitivity. On the other hand, pooled testing, in which samples from multiple donors are combined before testing, is preferred by many blood centers that need to process large number of donated blood units.

A better understanding of the prevalence of TTIs in blood donors can support medical communities and government agencies to manage the disease burden, develop strategies to evaluate the safety of the blood supply, and aid in providing preventive measures for the development of vaccination programs. There is scarcity in current epidemiologic studies available from the region on the prevalence of transfusion-transmitted infections using both serological and/or NAT methods for blood donors in Saudi Arabia (SA), exemplified in this study for Makkah region by King Abdullah Medical City, a tertiary care facility. In the present retrospective study, we evaluated the NAT prevalence and seroprevalence of HBV, HCV, and HIV among blood donors in Makkah from 2011 to 2014, and compared their trends with different regions of the country. Donor serological and molecular profiles were extracted to provide temporal trends associated with TTIs prevalence and state of infections. Our secondary objective was to realize the most suitable NAT format, without compromising the sensitivity of NAT results by using IDT or mini-pool testing.

Methods

Donor population

Blood donor records covering the period between January 2011 and December 2014 were analyzed with respect to screening outcome of HBV, HCV, and HIV serological and molecular NAT markers. In the course of the study, all 22,963 blood donors were volunteers, relatives or friends of the recipients. Professional paid donors are banned as per practice of law. Potential donors must satisfactorily answer a questionnaire and pass a physical examination performed by trained personnel. Those who were apparently healthy, are between 18-60 years old, and weigh above 55 kg were qualified for donation. At the end of blood collection, donor samples were obtained for serological and NAT testing. Donor consent was obtained for all sample screening. The gender in this study was not analyzed as <0.4% of the entire donor population were female.

Serological assays

Serum samples were tested for the presence of 1) hepatitis B surface antigen (HBsAg) using ARCHITECT HBsAg (Abbott Diagnostics), 2) total anti-Core antibody (anti-HBc) using ARCHITECT CORE (Abbott Diagnostics), 3) antibodies for hepatitis C using ARCHITECT anti-HCV (Abbott Diagnostics), and 4) antibodies for HIV using ARCHITECT HIV Ag/Ab Combo (Abbott Diagnostics). These Chemiluminscent Microparticle Immunoassays (CMIA) provide qualitative detection of all viral targets and were performed according to manufacturer's instructions. The immunology laboratory at KAMC also screens donor plasma for syphilis and human T-lymphotropic virus (HTLV). Malaria testing using rapid malaria antigen test for individual donation (OptiMAL-IT, Biorad) is done at hematology laboratory. However, since the objective of the study was to compare both serological and NAT prevalence of TTIs, namely, HBV, HCV and HIV; then data related to donor screening for syphilis, malaria, and HTLV will not be discussed herein.

Nucleic Acid Amplification Testing (NAT)

The HBV, HCV and HIV nucleic acids were routinely tested using the FDA-approved Cobas TaqScreen MPX test v2.0 on Cobas s 201 sysetm (Roche) following the manufacturer's instructions. It is a qualitative multiplex test that enables the screening and simultaneous detection of HBV DNA, HCV RNA, HIV-1 groups M and group O RNA, and HIV-2 RNA (HIV types cannot be distinguished) in pooled and individual donor plasma specimens.

HBV/HCV/HIV dilution studies

Ten samples with viral load of <20 IU/ml for each HBV and HCV and <50 copies/ml HIV were diluted in 1:2, 1:4, 1:6, and 1:8 dilutions using previously tested negative plasma (by ELISA and NAT). The diluted samples were tested by TaqScreen MPX test v2.0 on Cobas s 201 sysetm (Roche) following the manufacturer's instructions.

Statistical Analysis

All blood donor data was entered in a Microsoft excel sheet. Counts and percentages were provided for basic data description purposes. Data was analyzed using SPSS 16.0 statistical software package (SPSS Inc., Chicago, IL).

Ethics statement

This was an observational study. All donors were managed in accordance with normal laboratory practice. The Institutional Review Board at King Abdullah Medical City approved the current study.

Results

During the four year study period, the number of blood donors progressively increased by 133% from 3,090 in 2011 to 7,195 in 2014 (Table 1). There was a gradual decline in the percentage of infected (HBV, HCV, and/or HIV) donor blood based on combined serological and/or NAT screening between 2011 (8.3%) to 2014 (6.8%) (Figure 1), that is equivalent to 17% reduction. Of the total (overall) 22,963 donors screened during the four year period, 1,689 (7.4%) were infected by one or more blood transmissible infectious agent; therefore, blood donations were discarded and donors were permanently deferred. This also meant that approximately one out of every fourteen prospective donors was rejected due to potential risk of TTIs.

Individual analysis of HBV, HCV and HIV serological or nucleic acid markers in blood donors revealed a trend in their prevalence as shown in Table 1. There was a slight increase in the prevalence rate of hepatitis B surface antigen (HBsAg), a marker of transmissible HBV, from 0.7% in 2011 to 0.8% in 2012, but decreased again in 2013 to 0.6% and remained stable till 2014 with 0.7% as the overall average HBsAg during the four year study period. Prevalence of antibodies to hepatitis B core (anti-HBc), a marker to acute, chronic and resolved HBV infection, showed a 20% decline from 7.9% to 6.4% during the first

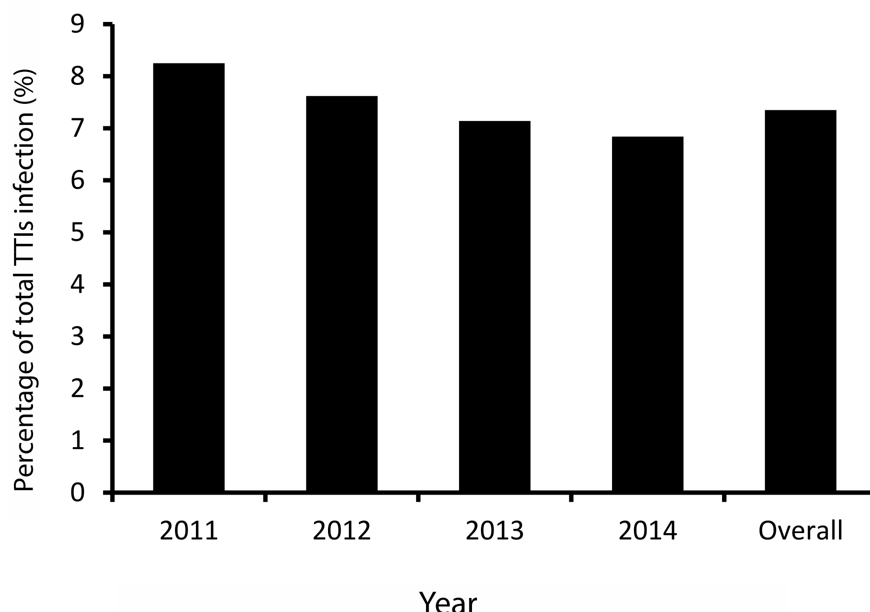

Figure 1: Temporal trend of total TTIs prevalence using combined serological and NAT screening. Trend in percentage of total TTIs infection detected by serological and nucleic acid testing of HBV, HCV, and HIV in blood donors with the overall from year 2011-2014.

Year	Total Donor No.	Marker													
		HBsAg		HBcAb		Anti-HCV		Anti-HIV		HBV DNA		HCV RNA		HIV RNA	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
2011	3090	20	0.7	244	7.9	6	0.2	3	0.1	21	0.68	0	0	0	0
2012	5731	47	0.8	408	7.1	23	0.4	2	0.04	47	0.85	2	0.03	1	0.02
2013	6947	43	0.6	442	6.4	43	0.6	7	0.1	46	0.66	7	0.1	4	0.06
2014	7195	44	0.6	454	6.3	30	0.4	4	0.06	50	0.69	2	0.03	1	0.01
Overall	22963	154	0.70	1548	6.7	102	0.44	16	0.07	164	0.72	11	0.05	6	0.03

Table 1: Temporal trend of serological and nucleic acid markers presented in Saudi blood donors. Trend in numbers and prevalence of individual HBV, HCV, and HIV serological and nucleic acid markers among blood donors in Makkah from 2011 to 2014.

three years from 2011 to 2013; whereas it remained unchanged with roughly 6.3% in the last two years between 2013 and 2014 giving an overall prevalence of 6.7%. The corresponding HBV DNA, a maker for acute or occult HBV infection, showed a similar pattern to HBsAg with a spike in its prevalence rate from 0.68% in 2011 to 0.85% in 2012 then dropped back to ~0.7% which is approximately the overall prevalence of HBV DNA amongst donor pool.

The prevalence of anti-HCV doubled from 0.2% in 2011 to 0.4% in 2012 and continued exhibiting an upward annual trend to 0.6% in 2013 resulting in 218% increase in three years. However, there was a decline of anti-HCV in 2014 to previously observed levels of 0.4%, which is almost identical to the overall anti-HCV prevalence of 0.44%. The corresponding molecular HCV RNA marker showed a comparable pattern to its serological counterpart with a continuous increase in the first three years only to decline back to similar levels of 0.03% seen in 2012. The overall HCV RNA prevalence was 0.05%.

Anti-HIV prevalence fluctuated greatly throughout the period under review. In 2012, the prevalence of anti-HIV almost halved as compared to 2011 only to peak back in 2013 to previously seen level of 0.1%. Following a second decline in 2014 to 0.6%, the overall prevalence of anti-HIV was 0.07%. The corresponding molecular HIV RNA marker showed a similar pattern to its serological counterpart with a steady increase in first three years only to fall back in 2014 to 0.01% presenting an overall HIV RNA prevalence of 0.03%.

Donor profiles which combine HBV, HCV, and HIV serologic markers with NAT markers were analyzed for all seropositive and/or NAT reactive donors in order to identify the status and prevalence of the infected donors. The patterns observed are summarized in Table 2. Acute or chronic HBV infection represented by HBV-DNA, HBsAg and antiHBc-positive donors made up 0.61% and has shown relatively a stable annual rate throughout the study period. Pre-seroconversion window period or occult infection indicated by presence of solitary HBV DNA was observed annually in limited numbers over a three year period with an overall prevalence of 0.04%. A consistent high prevalence of the multifaceted solitary Anti-HBc, indicating a state of previous infection, showed a 21% decline from 7.2% in 2011 to 5.7% in 2014 with an overall prevalence of 6%. We have observed Anti-HBc in combination with reactive HBV-DNA at fluctuating rates throughout the study period with an overall prevalence of 0.04% which could be indicative of low level carrier, early convalescent period remote HBV

	2011		2012		2013		2014		Overall	
Positive Marker	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
HBc-Ab	223	7.2	357	6.2	397	5.7	408	5.7	1385	6.0
HBc-Ab + HbsAg + HBV-DNA	18	0.6	39	0.7	40	0.6	44	0.61	141	0.61
HBsAg	2	0.06	8	0.1	3	0.04	0	0.01	13	0.05
HBc-Ab + HBV-DNA	3	0.1	4	0.07	1	0.01	2	0.03	10	0.04
HBV-DNA	0	0	4	0.07	2	0.03	4	0.06	10	0.04
HBc-Ab + HBV-DNA + HCV-RNA	0	0	0	0	3	0.04	0	0	3	0.01
Anti-HCV	6	0.2	21	0.4	39	0.6	28	0.4	94	0.41
Anti-HCV + HCV-RNA	0	0	2	0.04	4	0.06	2	0.03	8	0.04
Anti-HIV	3	0.1	1	0.02	3	0.04	3	0.04	10	0.04
Anti-HIV + HIV RNA	0	0	1	0.02	4	0.06	1	0.01	6	0.03

Table 2: Temporal trend of combined serological and NAT profiles presented in Saudi blood donors. Trend in numbers and prevalence of combined HBV, HCV, and HIV serological and nucleic acid profiles among blood donors in Makkah from 2011 to 2014.

infection, passive transfer of antibody, or occult infection as discussed in more detail later [4]. There were few solitary HBsAg seropositive cases reported with an overall seroprevalence of 0.04%. Early acute infection indicated by sole presence of HBV-DNA and HBsAg was not observed amongst blood donors throughout the study period.

There was a significant increase (189%) in solitary anti-HCV (negative HCV-RNA) donor profile indicating chronic HCV infection from 0.2% in 2011 to its peak at 0.6% in 2013. A significant decline in anti-HCV profile to 0.4% in 2014 resulted in an overall prevalence of 0.41%. There were sporadic positive anti-HCV and HCV-RNA profile cases observed between 2012 and 2014 indicating active HCV infection in those donors. There was no observation of occult infection or acute HCV infection represented by anti-HCV-negative/RNA-positive serological and molecular profile. However, there were three donors with dual HBV and HCV infections who had identical profiles positive for HBc-Ab, HBV-DNA, and HCV-RNA possibly indicating an acute HCV infection concomitant with a previous HBV infection.

HIV-infected donor profiles were observed in lower rates as compared to HBV and HCV infections. Solitary anti-HIV (negative HIV-RNA) profile ranged from 0.02% in 2012 to its peak in 2011 with 0.1%. This donor profile had a stabilized rate in the last two years identical to the overall prevalence at 0.04%. Few profile cases positive for anti-HIV and HIV-RNA were observed between 2012 and 2014 indicating active HIV infection in those donors. Acute HIV infection represented by anti-HIV-negative/RNA-positive profile was not observed amongst our donor pool.

A secondary objective of this study was to determine the most suitable NAT testing format by comparing individual donor testing versus screening in mini-pool. Thus, randomly selected 600 donor units were screened by both individual testing and in a 6-sample mini-pool (i.e. 100 pools). Nine NAT reactive (eight HBV-reactive and one HIV-reactive) individually tested units were identified using IDT format. However, using the mini-pool format, only eight of those same NAT-reactive units were identified in their respective pools and one case presented no reactivity (involving HIV). HIV-RNA quantitation performed using COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0 (Roche diagnostics), revealed detection of 70 copies/ml in this blood donor unit. This prompted us to perform dilution studies using HBV, HCV and HIV-positive samples with known viral loads to simulate the mini-pool NAT scenario. As shown in Figure 2, all ten samples for undiluted HBV (<20 IU/ml), HCV (<20 IU/ml), or HIV (<50 copies/ml HIV) were detected by NAT. At 1:2 dilution, nine (90%) were reactive for HBV, and eight (80%) for each HCV and HIV. When samples were tested at dilution of 1:4, reactivity was observed in only eight (80%) HBV, seven (70%) HCV, and six (60%) HIV samples. The critical dilution of 1:6, which accurately represented the mini-pool NAT format tentatively used in our lab, revealed significant reduction in HBV detection to seven (70%), HCV to five (50%), followed by HIV to 4 (40%). Final dilution of 1:8 reduced detection of all targets to 50% or less.

Discussion

The long-term morbidity and mortality associated with infections caused by hepatitis B and C viruses, as well as HIV have imposed a great burden on the health care system around the world including SA. It is imperative to monitor the prevalence of TTIs so as to assess the risk in donor pool, and by inference, the risk in general to Saudi population receiving the blood donations. Currently, there is a paucity of information about an updated burden of HBV, HCV and HIV in Saudi Arabia. The use of NAT screening to detect infections among blood donors that were undetected by serological tests can be more beneficial where seroprevalence of TTIs is high, as is the case in most developing countries. Indeed, screening of blood and blood components by dual testing strategy using serological assays and high sensitivity NAT helps in detecting the potentially infectious blood units in all phases of infection including pre-seroconversion “window period”. In Saudi Arabia, the national testing guidelines, developed following discovery of alarming rise in HBV infections in the late 1980s [5], recommended that all blood units must be screened for markers of transfusion-transmitted diseases (TTDs), including HBsAg, anti-HBc, anti-HBs (for all anti-HBc positive samples), anti-HCV, HIV I/II, HIV p24 antigen, and the human T-lymphotropic virus (anti-HTLV I/II), in addition to using a serological test for syphilis and malaria [6]. Because the screened seronegative donations are still at risk for TTIs, NAT has become compulsory by ministry of health in 2010. While there may be an adequate number of studies addressing the seroprevalence of TTIs in Saudi Arabia, there is a scarcity of TTIs NAT prevalence for HBV, HCV and HIV.

In this study, we characterized the prevalence and trend of HBV, HCV, and HIV serological and molecular nucleic acid markers in blood donors from the city of Makkah between 2011 and 2014. The overall serological prevalence of HBs-Ag, anti-HBc, anti-HCV, and anti-HIV during the period under study were 0.7, 6.7, 0.44, and 0.07% respectively. Molecular HBV-DNA, HCV-RNA, and HIV-RNA overall prevalence, on the other hand, were 0.72, 0.05, and 0.03% respectively. The overall prevalence of combined serological and/or NAT screening, indicating infection by one or more blood transmissible infectious agent, in our cohort of donors was 7.4% with the highest (8.3%) rate occurring in 2011 and lowest (6.8%) in 2014 .

Because our study covers a four year time frame, we were able to compare our results to other regions in the Kingdom where possible and to past published data (Table 3). Several studies published more than a decade ago reported 1.5-4% seroprevalence of HBV HBsAg in the central region of SA indicating a noticeable difference in HBV prevalence during recent years by comparison to other regions [7-9]. Similar to our data, HBsAg seroprevalence has been reported by recent studies including southwestern rural areas in SA revealing a 1.03% [10], 1.5% in the central city of Riyadh [11], as well 0.53-1.67% in the Eastern region [12]. However, a significantly higher 3.8% HBsAg seroprevalence has been reported in the southwestern region of Jazan [6], as well as 3% in the Northwestern region of Tabuk [13]. Jeddah, which is considered a neighboring city of Makkah, has a significantly higher HBs-Ag rate of 6.11% than all other regions based on available literature [14]. Thus, Makkah seems to boast one of the lowest HBsAg seroprevalence rates along with Taif, present in the same geographical region, at 0.33% [15]. We can only compare our HBV-DNA prevalence to recently published studies as NAT screening was introduced to SA in 2010; thus very scarce data is available in literature. Nevertheless, comparable to our result of 0.72% in Makkah, HBV-DNA prevalence by NAT testing has been reported as 0.83% in the western region of Taif [15], and 0.94% in the southwestern region [10]. These observations are consistent with the government's directives and efforts to reduce HBV infection by mandating vaccinations of healthcare workers and all Saudi children at school entry [11]. Although HBV seroprevalence in Makkah may be considered low, undesirable infection rates from various other regions still exist. The magnitude of regional variation in HBV infection present in SA may be attributed to 1) differential socioeconomic status associated with sanitation and standard of life, 2) blood transfusion practices, 3) awareness of safe clinical and social practices especially in rural areas with lower educational levels, and 4) compliance with childhood immunization against HBV.

The increased overall TTIs prevalence in our study is mainly attributed to the high 6.7% rate of HBV seropositive anti-HBc donor units. Most of rejected HBV seropositive donors were negative for HBsAg and positive for anti-HBc. HBcAb positivity with seronegative HBsAg status may be due to 1) false-positive results, or 2) evidence of

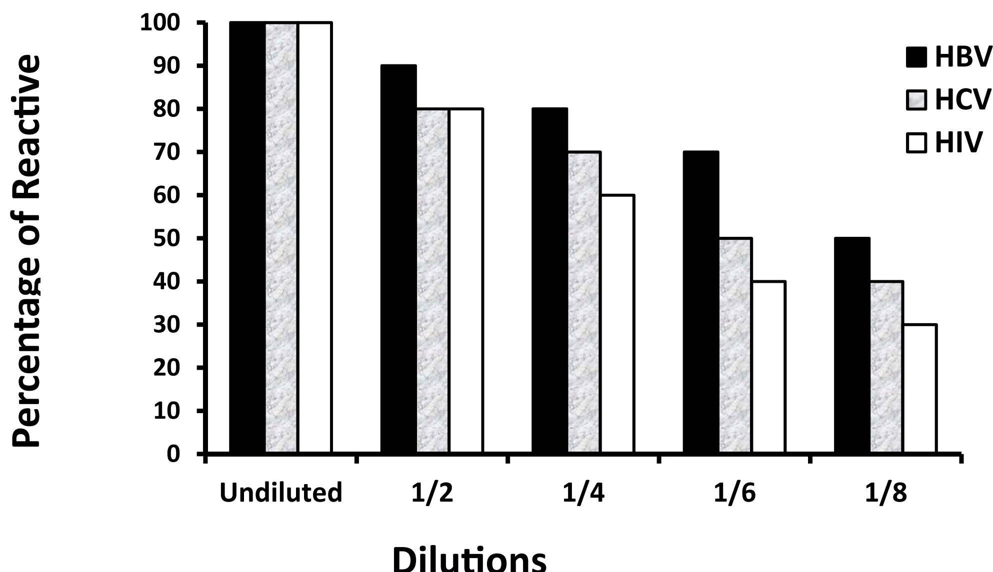

Figure 2: Effect of dilution on detection of low viral load HBV, HCV and HIV by NAT. Percentage of NAT detection following various dilutions of HBV-, HCV-, and HIV-positive samples with known viral load (<20 IU/ml for HBV and HCV, and <50 copies/ml HIV).

Province	Location	Sample Size	HBsAg	Anti-HBc	Anti-HCV	Anti-HIV	NAT HBV	NAT HCV	NAT HIV	Reference
Mekkah	Western	22,963	0.66%	6.7	0.44%	0.07%	0. 72%	0.05%	0.03%	Present study
Jeddah	Western	638;21,726; 55, 7813	6.11%	21.50%	1%	1%	NA	NA	0.46%	Redwan et al. [14] Fageeh [33]; Shobokshi et al. [30]
Taif	Western	600; 3,288	0.33%	11.5	0.63%	0.15%	0. 83%	0.20%	0.80%	Bamaga et al. [15]; Bamaga et al. [31]
Riyadh	Central	55,7813; 24,173	1.50%	NA	0.40%	NA	NA	NA	NA	Abdo et al. [11]; Shobokshi et al. [30]; El-Hazmi [8]
Dammam	Eastern	13,435; 13,443	0.53-1.67%	9.15%	0.59-0. 83%	0.29%	0.03%	NA	NA	Morsi [32]; Bashawri et al. [12]
Jazan	Southwestern	29,949	3. 8%	5.70%	0. 41%	NA	NA	NA	NA	Abdullah [6]
Aseer	Southwestern	6,698	1.03%	6.14%	0.069	NA	0.94%	NA	NA	Ibrahim et al. [10]; Alshehri [29]
Tabuk	Northwestern	3,192; 55,7813;	3%	18.7%	0.70%	NA	NA	NA	NA	El-Beltagy et al. [13]; Shobokshi et al. [30]
(NA=Not available in literature)										

Table 3: Comparison of TTI prevalence rates using serological and NAT markers among different regions of KSA.

acute, chronic or resolved HBV infection that remains detectable for life. Furthermore, blood that is free of HBsAg but has high-titer anti-HBc in the absence of antibodies against hepatitis B surface antigen (anti-HBs) could have traces of circulating HBV DNA which is thus potentially transmissible, as has been demonstrated by contagion occurring through blood transfusion from donors who were only HBcAb (+) [4,16-19]. The high anti-HBc seroprevalence seems to be an extant phenomenon in different Saudi regions. Recent studies in southwestern SA revealed a similar 6.14% and 5.7% HBcAb seroprevalence, respectively, as compared to our data [6,10]. However, alarming rates have been reported in the northwestern region of Tabuk with 18.7% [13], and in Jeddah with 21.5% [20], indicating regional variation of HBcAb seroprevalence. The high HBcAb seroprevalence in these two cities, Jeddah and Tabuk, is concomitant with high HBsAg rates as shown in Table 3 likely indicating acute or chronic HBV infection in those donor pools, even though NAT studies were not performed to determine HBV-DNA levels.

In order to manage the high anti-HBc positive donor units at our center, we implement the policy of rejecting all HBV core antibody positive donor units. In other regional blood banks in SA, positive anti-HBc units are further evaluated for HBV surface antibodies before decision to discard the suspected seropositive units. In low prevalence countries, like the USA and Japan, blood donors are screened for both HBsAg and antibody to anti-HBc [2,21]. Individuals positive for either are disqualified because of ongoing infections or possible occult HBV infection. The strategy of combined HBsAg and anti-HBc screening virtually eliminates blood-transmitted HBV, with the rare exception of donations in the early phase of the window period when all serological markers are still negative [22]. We do recognize that some of the anti-HBc positive donor units may be false positive. In fact, a major problem facing blood banks around the world is the loss of donors who test repeatedly reactive in screening enzyme immunoassays but are not confirmed as positive upon further testing [23,24]. Asian countries for example have intermediate or highly endemic HBV infection where 16-90% of adults had either past or ongoing HBV infections [25]. A study by a Malaysian group showed that 1,388 donor samples tested by serology methods were in fact non-reactive by NAT [26]. These samples were confirmed to be “false-reactive” on confirmatory serological tests. Similarly, many studies observed low specificity of total anti-HBc tests when using enzyme immunoassays [27]. Nevertheless, this serological marker has increased the positive predictive value for the identification of truly HBV-infected individuals. Also, there still exists a significant number of anti-HBc positive donor cases observed in our study to ignore the high prevalence of this serological marker amongst Saudi population as similarly reported by other regional studies mentioned in Table 3.

In contrast to HBV, HCV seroprevalence seems to be in steady rates as our study reported 0.44%, which is comparable to past studies more than a decade ago [8,9], and to more recently published data [6,28-30] showing rates of 0.4-1.1% during both time periods. However, we observed a much lower 0.05% prevalence of HCV-RNA as compared to the city of Taif, considered within the same geographical region as Makkah, where a higher rate of 0.2% has been reported [31]. To our knowledge, no other studies are available addressing HCV-RNA prevalence in other SA regions. Similarly, while there is limited data in literature to enable comparison of HIV seroprevalence amongst different SA regions, scarce studies exist with respect to HIV-RNA prevalence. The overall seroprevalence of anti-HIV (0.07%) remains lower than previously reported as 0.29% in eastern region of SA [32], an elevated 1 % in western region of Jeddah [33], and 0.15% in neighboring city of Taif. HIV-RNA shows a similar trend in its molecular prevalence with 0.46% and 0.8% reported in western region, and what may be the only Saudi prevalence studies reporting HIV-RNA available in literature. Nevertheless, Makkah has a significantly lower 0.03% HIV-RNA prevalence than its surrounding cities found in the western region.

Our chief interest lay in understanding the serological and molecular profiles of blood donors presented in our center. To our knowledge, no Saudi or regional studies have addressed donor profiles hindering our ability to make national level comparisons. However, similarity with data available from other countries could be a starting point in hope of analogous prospective Saudi studies. First, our data has revealed a significant number of donors positive for anti-HBc (negative for both HBsAg and HBV-DNA) represented the highest (6%) donor profile of TTI infection, but has seen a gradual decline during the four year study period. The interpretation of this profile depends on testing for antibody to hepatitis B surface protein (anti-HBs), which was not performed by our center for donor screening. Nevertheless, positive anti-HBc with negative anti-HBs units may be in remote HBV infection, occult infection, early convalescent period, or even have low-level carrier or passive transfer of antibody [4]. On the other hand, donor units with positive anti-HBs would be considered in a state of previous infection with immunity or occult infection. The anti-HBc levels (with or without anti-HBs) observed among our blood donors is significantly higher than reported in the US at 0.32% [4], Canada at 0.47% [34], and Northern Europe at 1.4% [35]. Comparable levels on the other hand were observed at 7.8% in Egypt [36], 8% in Iran [37], and 17.6% in Pakistan [38]. Second, data has revealed HBc-Ab-positive/HbsAg-positive/ HBV-DNA positive as the second highest (0.6%) donor profile of TTI infection indicating a significant number of donors have either acute or chronic HBV infection with steady rates observed from 2011 to 2014. This is also significantly higher than reported at 0.002% in the US [39], and 0.02% in Northern Europe [40]. Other developing countries have prevalence rates of 4.2% in Egypt [41], 2.6% in Pakistan [42], and 7.5% in Nigeria [1]. Thus, Makkah boasts much lower acute and chronic HBV infection than other developing countries but comes short on attaining the level present in developed countries.

Chronic HCV infection represented by solitary anti-HCV marker was the third highest TTI donor profile observed in the study at 0.4%. These anti-HCV positive donors lacked detectable HCV RNA which could be an indication of viral clearance rather than chronic persistent infection. It is interesting to note the occurrence of co-infections in three donors all involving dual HBV and HCV with the same profile, HBc-Ab+ /HBV-DNA /HCV-RNA. The HBsAg is likely absent in these donors due to mutations such as the pre-S deletions that could block export of this antigen, or it may be due to HCV core protein interference with the replication of HBV and synthesis of viral proteins [43]. Anti-HCV prevalence rate observed in our study is comparable to that observed at 0.5% in Iran [44], 0.46% in Argentine [24], 0.86% in Nigeria [1], and 0.51% in China [24]. In contrast, other surrounding Arab countries in the region showed a significantly higher seroprevalence of HCV than Makkah including Yemen at 2.7 % [45], Oman at 1.2% [46], Iraq at 3.2% [47], Egypt at 5-25% [48], and Pakistan at 5% [42]. Developed countries like the US on the other hand still boast low HCV seroprevalence at 0.02% [21].

Finally, one donor profile represented a discordant outcome at low prevalence of 0.05% is solitary HBsAg. Kleinman et al. previously reported that 4.1% of HBsAg reactive samples lacked anti-HBc, and were in fact near the cutoff value [49]. These samples tested HBV-DNA negative, inconsistent with pre-seroconversion window period infection and therefore were interpreted as false-positive HBsAg

results. Indeed, the thirteen donor units reported with solitary HBsAg in this study were near the cutoff value of the assay and were possibly false positive. Another plausible explanation for these sporadic false-positive cases could be the low-level carryover of plasma or serum from a chronic HBsAg carrier of an adjacent test well causing dilutional low-level cross contamination [4].

One of the major advantages of NAT is the reduction of inadvertent transmission of HIV, HCV and HBV due to improved detection of window period infections when antibodies are still undetectable. For example, HBV can still be transmitted by blood from asymptomatic donors with acute HBV infections who have not yet developed HBsAg or anti-HBc, but are NAT-reactive for HBV DNA [50]. In our study, all ten identified NAT reactive/seronegative cases involved HBV reactivity making the combined NAT yield (NAT reactive/seronegative) 0.04% (1 in 2,296 donations). This is significantly higher than other developed countries like the US where HBV DNA pre-seroconversion rate (HBsAg- and AntiHBV-negative, HBV-DNA positive) was found at 0.0002% (1:610,488) [4], but similar to other developing countries such as India where the combined NAT yield for HBV, HCV and HIV was reported to be 0.034% (1 in 2,972 donations) and 0.038% (1 in 2,622 donations) by two independent studies [51,52]. In a study from Egypt, five window period HCV donations were identified among 15,655 first time donors (yield 1:3,100) [53]. In our study, there was no observation of any acute infections of HCV or HIV comprising the viremic pre-seroconversion phase. Also, there are no available studies in literature, from other regions in SA or neighboring countries, which use NAT screening to determine TTI prevalence during window period that enable comparison with our data.

Due to the financial impact of individual donor testing (IDT), we opted to explore mini-pool screening at our center, which has the advantage of being cost effective even though existent limitations include 1) the whole size being blocked until the NAT report is available, 2) reactive pooled tests will be retested and resolved individually adding additional step of handling, time for testing and hence delay in release of units; and most important 3) the virus inoculum size may vary by route of infection, possibly affecting viral load during the window phase such that pooled or diluted sample approaches may be less effective at detecting viremia in early infection. In our study, random screening of 600 units presented one RNA-positive HIV subject when tested individually, but presented non-reactive result when tested in a pool of six suggesting the sensitivity of NAT, even in mini-pools, may approach the threshold for infection. Indeed, dilution of HBV-, HCV- and HIV-positive samples has shown significant decrease in NAT detection, particularly at 1:6 which simulated the mini-pool format tentatively used in our lab. The sensitivity of NAT assays has been previously examined by various studies showing limit of detection (LOD) of 43 IU/ml or 25 copies/ml for HIV [54,55]. In our study, the arbitrarily selected HIV-positive donor blood unit was diluted six fold (~12 copies/ml) which placed it below LOD, and therefore it was undetected by the mini-pool assay. This was concerning as HIV-positive plasma with a viral load of less than 40 copies/ml has been demonstrated as the threshold for viremia that is indicative of ongoing virus replication associated with a risk of virologic rebound [56]. Furthermore, other studies comparing testing sensitivity by IDT versus mini-pool has shown that 67% of samples with low viral load were missed by mini-pool testing [52]. In the US, mini-pool testing remains widely used as HBV is not endemic, anti-HBc testing is in place, and HBV vaccine is universally recommended [55]. However, the US FDA issued a guidance, without dictating which NAT testing format to use (IDT or mini-pool), requiring HBV-DNA, HCV-RNA and HIV-RNA detection by NAT meets a minimum sensitivity (e.g. 100 IU/ml for HBV) [55]. In SA, there are no governmental or national laws dictating the format of NAT testing as IDT or mini-pool units nor laws that address the minimum expected sensitivity. In fact, because of the high cost of introducing NAT screening of blood donors in SA, many laboratories opt to use mini-pool testing. However, in a country where pre-seroconversion rates for TTIs is higher than developed countries as shown by our results, national guidance banning mini-pool testing should be considered.

We recognize that our study had limitations worth mentioning and may be biased. The ideal condition to carry out a prevalence study is to sample the general population [24,57,58]. The donors included in this study represent the Western region of SA and may underestimate both the NAT and serological prevalence as the blood donor candidates are pre-selected based on a questionnaire and a physical exam, and blood is drawn from apparently healthy individuals at low risk of having TTIs. Symptomatic individuals, or those with prior knowledge of infection, would selectively opt out from blood donation.

On the other hand, one can argue the results may be overestimated given that, as in most studies performed in blood banks including our center, positive screening tests are not confirmed and have a variable percentage of false positives [24]. To address this, comparative analysis studies performed on general population and blood donors to evaluate TTIs prevalence have been previously published. Petrovic et al. showed that the ratio of prevalence between the general population and blood donors ranges from 1.17 to 1.70 for HBsAg and from 1.25 to 3.00 for anti-HCV [59]. Similarly, in a study conducted by Karaosmanoglu et al., a ratio of 1.89 was observed when comparing the prevalence of HBsAg among blood donors and healthy people who required a premarital screening [60].

Another limitation to present data is that less than 0.4% of donor population was comprised of females as blood donors in SA are traditionally male. This is consistent with other Saudi studies habitually showing almost all male predominance and females comprise <1% of blood donors [8,10]. Therefore, these male-dominant blood donor studies may under- or over-estimate disease prevalence. Age was not analyzed either as all the blood donors in our study were between the ages 19-50 and most prevalence rates observed (with the exception of anti-HBc) were ≤0.6% (Table 2), indicating low TTI infection to start with. Nevertheless, HBV vaccination program of infants at birth was initiated in SA in 1989 and for children in schools in 1990, which means people younger than age of 30 would have been vaccinated as children at this time and expected to have lower HBV infection rates. Furthermore, many studies demonstrated with consensus that increased age correlates with increased HBV infection likely due to more exposure [8,24,25]. Finally, the analysis was restricted to infections detected by NAT or serological tests which may not detect highly divergent TTI variants. However, given efforts of test manufacturers and regulators to ensure production of sensitive blood donor screening assays, we believe this issue has limited impact on our findings.

Conclusions

In spite of the limitations discussed above, we believe that the present study may still contribute invaluable data to better understand the current epidemiology of TTIs in the Saudi community. To our knowledge, there is no published study collectively comparing HBV, HCV, and HIV serological and nucleic acid markers amongst Saudi population. More updated and similar descriptive studies addressing the prevalence and trends of HBV, HCV, and HIV should be performed in different provinces and regions of SA, especially related to nucleic

acid markers. In turn, a prospective cross-sectional study in SA will help determine the trend and profile of TTIs in the country, which could reflect changes in population risks, and produce a reliable index for policy making.

Conflict of Interest

The authors indicated no potential conflicts of interest.

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