Prenatal Screening of Potential Infectious Diseases in Manitoba

By

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Abstract

Perinatal infections are associated with significant morbidity and mortality for both pregnant women and their infants, including while *in utero*. Prenatal screening for potential infectious diseases can effectively prevent MTCT infections. It allows both timely and suitable medical interventions when required. In Manitoba, prenatal screening for Rubella, Hepatitis B Virus (HBV), Human Immunodeficiency Virus (HIV), *Treponema pallidum*, *Chlamydia Trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) is recommended for all pregnant women and in each pregnancy. The research described in this thesis assesses the current adherence to the Manitoba prenatal screening guidelines. Data consisted of prenatal screening tests conducted at Cadham Provincial Lab (CPL) for the time period of 2006 to 2011.

Approximately one fifth of pregnant women did not receive any form of recommended prenatal testings'. Adherence to prenatal screening guidelines varied by type of infection, age of women and area of residence.

Overall, Rubella, HBV and syphilis prenatal screening were requested more frequently than HIV, CT and GC. From year to year, a significant improvement of HIV prenatal screening uptake was observed. Rubella, HBV and syphilis screening declined while GC and CT screening remained stable.

Among screened women, HIV testing was requested significantly less frequently in the youngest <15 and oldest >45 age groups versus other age groups. Women >45 years old also received less GC and CT screening. A year-

to-year increase in HIV and GC screening was observed in pregnant women aged 15-25, 26-35, and 36-45 years old.

Although HIV screening uptake increased over time among residents of Brandon and rural areas, the overall HIV screening test was still higher among residents of Winnipeg versus other areas. Similarly, residents of Brandon and rural areas were tested less frequently for CT infection. A significant improvement in GC screening among residents of Winnipeg and rural areas was observed.

The results described in this thesis demonstrates inconsistent adherence to provincial guidelines – creates higher risk areas and population subsets for congenital infections.. The results also demonstrate the importance of promoting testing of this type among pregnant women. Improvement and enhancement of current practice is required to reach standard, satisfactory and appropriate adherence to screening guidelines. Ongoing periodic assessments are suggested to continually document and monitor uptake and adherence to recommended prenatal screening in Manitoba.

Contributions

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Dedication

I would like to dedicate my work to:

My parents (Nihad Miski and Ali Faizo), my lovely sister (Esraa) and to my great brothers (Dr. Eyad, AbdulRahman and Osama) who were always beside me by their unconditional support, encouragement and love.

My parents in law (Aisha and Abdulaziz) for their endless support of my dream.

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List of abbreviations:

ACOG: American College of Obstetricians and Gynecologists

AIDS: Acquired Immunodeficiency Syndrome.

ALT: Alanine Aminotransferase.

ART: Antiretroviral Therapy.

CDC: Centers for Disease Control and Prevention

CPL: Cadham Provincial Laboratory.

CRS: Congenital Rubella Syndrome

CT: *Chlamydia trachomatis*.

ELISA: Enzyme-Linked Immunosorbent Assay

FTA-ABS: Fluorescence Treponemal Antibody Absorption Test

GC: *Neisseria gonorrhoeae*

HAART: Highly Active Antiretroviral Therapy

HBV: Hepatitis B Virus

HBsAg: Hepatitis B Surface Antigen

HIPC: Health Information Privacy Committee

HIV: Human Immunodeficiency Virus

HREB: Health Research Ethics Board

IDU: Injection Drug Use.

ISB: Information Systems Branch

LIMS: Laboratory Information Management System.

LLTO: Laboratory Liaison Technical Officer.

MMR: Measles –Mumps- Rubella.

MSM: Men who have Sex with Men

MTCT: Mother to Child Transmission

NAAT: Nucleic Acid Amplification Test

PCR: Polymerase Chain Reaction

PHAC: Public Health Agency of Canada

PHIN: Personal Health Information Number

PID: Pelvic Inflammatory Disease

RHA: Regional Health Authority

RPR: Rapid Plasma Reagin

STBBI: Sexually Transmitted and Blood Borne Infection(s).

STI: Sexually Transmitted Infection

TP-PA: *Treponema pallidum* Practical Agglutination Test

UNAIDS: United Nations Program on HIV/AIDS

USPSTF: United States. Preventive Services Task Force

VDRL: Venereal Disease Research Laboratory Test

VSA: Vital Statistics Agency

WHO: World Health Organization

Introduction

Mother to child transmission (MTCT) of both viral and bacterial infections from pregnant women to their fetuses is considered a major cause of infant morbidity and potential mortality (Schmidt *et al*., 2009). However, the risk of MTCT infections can be considerably minimized or completely eliminated using various prevention strategies (Schrag *et al*., 2003). Over the last few decades, medical interventions to avert the transmission of certain pathogenic viruses and bacteria, including hepatitis B virus (HBV), human immunodeficiency virus (HIV), rubella virus, *Treponema pallidum*, *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) during pregnancy, labor and delivery have been implemented to prevent or reduce the burden of infections associated with these pathogens among babies born to infected women (Schmidt *et al*., 2009). For instance, congenital rubella syndrome (CRS) is a vaccine preventable infection, prenatal HIV infection can be prevented by administering antiretroviral therapies (ART) in addition to other medical interventions for both infected mothers and fetuses, and vertical transmission of HBV can be prevented by administering vaccine and hepatitis B immunoglobulin (Schrag *et al*., 2003).

In Canada and many other countries, prenatal screening is a routine procedure that is offered to all pregnant women during pregnancy and considered a critical part of protection against MTCT infections (Schrag *et al*., 2003 and Giraudon *et al*., 2009). The aim of prenatal screening of infectious diseases is to identify and confirm the presence of existing maternal infections and therefore allow for the provision of early and suitable medical interventions

as required (Schrag *et al*., 2003). Yet, for a variety of reasons, some pregnant women do not receive prenatal screening tests early in pregnancy and accordingly this increases the risk of MTCT infection among newborns. Therefore, a current assessment on the prenatal screening adherence rates would be of great importance to deliver up-to-date information for potential improvement of provincial screening programs.

1.1 MTCT Infections

Infections are common during pregnancy due to the several changes that occur in a woman's immune system (Mor and Cardenas., 2010). Although some aspects of innate immunity are enhanced, cell-mediated immunity is reduced in pregnant women (Mor and Cardenas., 2010). Suppression of cell mediated immunity allows fetal retention (Mor and Cardenas., 2010). However, it makes the pregnant woman more susceptible to infections (Mor and Cardenas., 2010). Infections during pregnancy are considered a primary cause of preventable morbidity and potential mortality among newborns (Schrag *et al*., 2003). The potential risk of acquiring infections in pregnant women is associated with both the type of pathogen and the site of infection (Mor and Cardenas., 2010).

MTCT infections, described as infections transmitted from an infected mother to an infant during pregnancy, labor or at delivery are associated with the presence of untreated sexually transmitted infections (STIs) (Schrag *et al*., 2003). According to the World Health Organization (WHO), the presence of reproductive

health consequences and infections around the world might be resulted from untreated STIs (WHO, 2013). Pre-term birth, low birth weight, stillbirth and death are all examples of significant outcomes that affect fetuses and infants born to infected women (Heather and Monica., 2007). Immature immune systems in fetuses and newborns also make them especially vulnerable to acquired infections such as HIV, HBV, rubella, syphilis, CT and GC (Glezen and Alpers., 1999, Siegrist and Lambert., 1998). The impact of maternal and congenital infection is significant. In 2008, over 1.3 million cases of untreated syphilis-infected pregnant women were reported by the WHO worldwide (WHO, 2013). Of this number, 520,000 cases resulted in serious outcomes such as stillbirth and neonatal death (WHO, 2013). Moreover, up to 50% of infants born to untreated GC or CT-infected mothers develop a serious eye infection (WHO, 2013). Due to this condition, it is estimated that around 1000–4000 newborn babies become blind worldwide yearly (WHO, 2013). Additionally, pneumonia can occur in up to 10–20% of infants born to mothers with a CT infection (WHO, 2013).

1.2 Prenatal screening program

In general, screening is a public health program that can consist of a question or a screening laboratory test to detect and identify people at risk of infections who can then be helped by the administration of further diagnostic tests, investigations or treatments to prevent a particular infection and its consequences (UK National Screening Committee., 1998). Screening of this kind is applicable in the case of pregnancy to reduce the risk of MTCT infections. The

availability of information about infections, screening tests, required treatments and the cost effectiveness of the screening process should all be taken into consideration when deciding whether to screen for infectious diseases (Wilson Jungner., 1968).

A prenatal screening program is applied routinely to all pregnant women early in their pregnancy (Schrag *et al*., 2003). Adherence to the guidelines of prenatal screening in conjunction with suitable medical interventions provides a significant clinical and diagnostic benefit in limiting and preventing MTCT of infections (Schmidt *et al*., 2009). However, it has also been revealed that positive test results for STIs may have a negative psychosocial impact (Niccolai *et al*., 2008 and Piercy., 2006). The feelings of shame, stigmatization and guilt in addition to other negative feelings are examples of potential psychosocial consequences of prenatal screening (Niccolai *et al*., 2008 and Piercy., 2006). Therefore, the benefit of a prenatal screening program must be carefully weighed against its risks.

In Manitoba, several prenatal screening tests for bacterial and viral infections are routinely offered. Serological approaches are requested for screening of *Treponema pallidum* (specific and non-specific antibodies), rubella IgG, and hepatitis B surface Antigen (HBsAg). Molecular-based techniques are performed to detect the presence of CT and GC. Also, an HIV screening test is routinely offered to all Manitoban pregnant women, unless the patients choose to opt out of the test. Other tests might be requested based on additional risk factors identified on assessment. Women with ongoing behavioral risk factors,

those only screened late in their pregnancy or not offered/presenting for prenatal care are at increased risk of transmitting infectious agents to their infants.

1.3 Viral Infections

Viral infections during pregnancy are major causes of both maternal and fetal morbidity and mortality (Gilbert, 2002). In general, viral infections can be transmitted to the neonate transplacentally, perinatally when infants are in contact with vaginal secretions or blood during delivery, or postnatally from breast milk (Gilbert, 2002). Clinical manifestations of neonatal infections vary depending on the viral agent and gestational age at exposure time (Gilbert., 2002). Additionally, the risk of infection is often inversely related to gestational age at acquisition (Marion, 2010). It is important to screen pregnant women for the presence of viral infections during their pregnancy to disrupt MTCT.

1.3.1 Rubella Infection:

Rubella is a viral infection caused by rubella virus. The virus is classified within the genus *Rubivirus*, family *Togaviridae.* The viral genome is comprised of an enveloped single RNA strand. Humans are the main reservoirs for rubella virus (De Santis *et al*., 2006). Hosts acquire the infection mainly through exposure to nasopharyngeal secretions that contain infectious particles (Richardson *et al*., 2001). The disease is usually mild and complications are rare

although thrombocytopenia and encephalitis have been reported (Edlich *et al*., 2005). Congenital infection is another important route for rubella virus transmission if women are not immunized (De Santis *et al*., 2006). During pregnancy, rubella virus infection can lead to several devastating outcomes such as stillbirth, miscarriage, and CRS (Frij *et al*., 1988). A number of ophthalmologic, neurologic, and cardiac abnormalities have been reported in infants with CRS (Frij *et al*., 1988). Large quantities of infectious particles are secreted in the urine of infants with CRS and, thereby, can be an important source for rubella virus infection (Frij *et al*., 1988).

1.3.1.1 Rubella epidemiology:

Although rubella is considered a preventable infection due to the presence of a highly effective vaccine, the disease remains endemic in some countries (Heymann., 2008).

In Canada, the number of rubella cases per year was about 5300 cases from 1971 to 1982 (Public Health Agency of Canada (PHAC)., 2006b). In 1983, the measles–mumps-rubella (MMR) routine infant immunization program was introduced (PHAC., 2006b). This has led to a dramatic decrease in the number of rubella cases per year. From 1998 to 2004, the annual number of rubella cases in Canada was less than 30 cases (PHAC, 2006a). Three CRS cases or less have been reported each year from 2000 to 2004 (National Advisory Committee on Immunization., 2006). A large outbreak of 1 per 100,000 rubella-infected

cases occurred in 2005 (PHAC, 2013b). From 2006 to 2011, the rate of rubella cases showed a significant reduction to 0.003 per 100,000 populations (PHAC, 2013b).

In Manitoba, since the 1990s, rubella outbreaks have been rare with the exception of a large outbreak that occurred in 1997, probably due to an early selective immunization program (PHAC, 2006b). Three rubella cases were reported from 2007 and 2009 (PHAC, 2013b). Congenital rubella cases are rare in Manitoba, with only three reports from 1991 to 2009 (PHAC, 2013b).

1.3.1.2 Rubella laboratory screening at CPL:

The following protocol is used for rubella laboratory diagnosis of pregnant woman who have exposed to rubella infection in Manitoba. A prenatal sample is collected 7 to 10 days post-exposure and tested for the presence of IgG to determine the immune status of the patient. No further laboratory diagnosis is required for pre-immunized patients who are positive for IgG. When IgG is absent another sample is collected approximately two weeks after the first specimen, and tested for the presence of IgM. If IgM is detected, another detection assay such as NAAT or culture is requested to confirm a case of acute rubella infection. If the patient lacks IgM, a third specimen is collected two weeks after the second sample, and tested again for both IgM and IgG. Absence of both immunoglobulins indicates that the patient has not acquired rubella infection. If both immunoglobulins are present, a case of acute infection is confirmed. If only

IgM is present, a confirmatory test is requested in order to confirm an acute infectious case (Communicable Disease Management Protocol., 2010).

For CRS cases, a serum specimen is collected at birth and tested for IgM, or a respiratory specimen is tested by cell culture or NAAT for rubella virus. Positive serologic test in the absence of recent immunization, isolation of the virus, or detection of viral nucleic acid means that the infant is likely infected If tests are negative, another sample is collected 4 weeks after the first one and retested for the presence of IgM. The presence of IgM confirms the CRS case, whereas the absence of IgM indicates an uninfected infant. Diagnosis of CRS using IgG antibody is not recommended for infants since mother's IgG antibodies can pass to their infants in uterus and gives positive IgG result (Communicable Disease Management Protocol., 2010).

1.3.1.3 Treatment and prevention of rubella infection

Administration of immunoglobulin has been proposed for pregnant women who are exposed to rubella during pregnancy (Remington and Klein., 2001). However, this treatment does not decrease the risk of fetal infection and subsequent CRS (Remington and Klein., 2001). Currently, there is no specific effective treatment for rubella infection. It can be prevented using a routine childhood immunization program with live attenuated vaccines (MMR vaccine) before a woman becomes pregnant (Bozzo *et al*., 2011). This vaccine is usually given in two doses: the first dose at 12 to 18 months of age and the second dose

prior to school entry (National Advisory Committee on Immunization., 2006). Receiving MMR vaccine during pregnancy is contraindicated and therefore, it is recommended that all women of reproductive age receive the MMR vaccine prior to pregnancy to protect future pregnancies rather than the current one (Bozzo *et al*., 2011).

1.3.1.4 Prenatal screening for rubella

In addition to the availability of effective childhood vaccination, prenatal screening of susceptible women of childbearing age is also an important strategy for the elimination of CRS (Robinson *et al*., 2006). The aim of prenatal screening is to identify women with no documentation of either rubella immunization or rubella seropositivity (Robinson *et al*., 2006). Due to concerns about possible teratogenicity, use of MMR vaccine is not recommended during pregnancy (Kroger *et al*., 2006). Therefore, supportive guidance is given to susceptible cases during pregnancy and one dose of rubella vaccination is given postpartum to protect future pregnancies (Robinson *et al*., 2006). In Canada, the program of prenatal screening also covers pregnant women who are new to the country (Banerji *et al*., 2005).

1.3.2 HIV and Acquired immunodeficiency syndrome (AIDS):

HIV mainly targets macrophages and T-helper lymphocytes although numerous cell types have been identified as potential targets for HIV (Chan and Kim., 1998). Upon infection, the viral genome is integrated into the host's genome and replicates during the cell cycle leading to lifetime viral persistence (Chan and Kim., 1998). Progressive destruction of immune cells makes HIV-infected individuals vulnerable to a wide range of opportunistic infectious agents (Chan and Kim., 1998).

HIV is primarily transmitted between susceptible and infected individuals via sexual contact (e.g., oral, vaginal, and anal) (Fowler *et al*., 1997). Various precautions (e.g., use of condoms) may reduce the risk of sexual transmission of HIV, although it does not completely eliminate it (Holmes *et al*., 2004). Injection drug use (IDU) is another source of HIV transmission (Fowler *et al*., 1997). Individuals who share unsterile needles and/or syringes with HIV-infected patients are at a high risk of HIV infection (Fowler *et al*., 1997). It was reported that approximately 19 percent of HIV cases in Manitoba from 1997-2008 are related to IDU (Manitoba Health., 2008). Transfusion of HIV-infected blood and transplantation of HIV-infected tissue or organs are other potential sources for the infection (Fowler *et al*., 1997). Nosocomial infection has been reported although the risk of transmission remains low (Fowler *et al*., 1997). HIV pregnant women can transmit the infection to their fetuses during pregnancy, delivery or labor (Fowler *et al*., 1997). The probability of MTCT increases when no antiviral treatment is taken during pregnancy (Wiktor *et al*., 1997). The stage of maternal

disease, viral load, and phenotype of the virus are other factors that may increase or decrease the risk of HIV transmission (Bulterys *et al*., 2004). HIV-infected mothers can also transmit the infection to their infants through breastfeeding (Bulterys *et al*., 2004).

1.3.2.1 HIV epidemiology:

Worldwide, as of 2012, approximately 35.3 million people were infected with HIV (United Nations Program on HIV/AIDS (UNAIDS)., 2013). Statistics show that the number of newly infected people in 2012 is lower by 33% versus new HIV cases reported in 2001 (UNAIDS., 2013).

In Canada, data for 2011 shows that there are nearly 71,300 people infected with HIV (PHAC., 2012b). Of these, 3,175 people were newly infected with HIV in 2011 (PHAC., 2012b). It has been shown that the number of infants exposed prenatally to the virus has increased from 181 in 2004 to 243 in 2010 (PHAC., 2011). This number declined to 230 in 2011 (PHAC., 2011).

In Manitoba, the number of newly HIV infected people decreased from 122 in 2010 to 80 in 2011. Thirty nine percent of these infected cases were reported in females (Manitoba Health., 2011). In addition, 70% of newly infected individuals were residing in Winnipeg (Manitoba Health., 2011). The major risk group experiencing HIV infection in Manitoba is considered to be men who have sex with men (Manitoba Health., 2011).

1.3.2.2 Laboratory diagnosis of HIV in pregnant women and testing options at CPL:

There are three testing options prescribed for HIV infection in Manitoba: nominal, non-nominal, and anonymous testing (Communicable Disease Management Protocol., 2010). Anonymous HIV testing involves the use of an anonymous code to represent the tested person instead of the patient's name. This type of testing is not considered suitable for prenatal testing (Communicable Disease Management Protocol, 2010). Non-nominal testing is a test where demographic information on a patient is used to generate a code that is then used for sample identification within the laboratory (Communicable Disease Management Protocol., 2010). This test is only available upon patient request (Communicable Disease Management Protocol., 2010). Nominal testing is the default name-based test where the tested person's name is documented on the requisition associated with the sample (Communicable Disease Management Protocol., 2010). This latter test is used for prenatal testing (Communicable Disease Management Protocol., 2010).

Both screening and confirmatory assays for HIV are based on detection of HIV-specific antibodies (Communicable Disease Management Protocol., 2010). ELISA (Enzyme-Linked Immunosorbent Assay) technique is applied as a HIV-screening test whereas Western blot is the HIV-confirmatory assay (Communicable Disease Management Protocol., 2010). A case of HIV is identified when both ELISA screening test and Western blot confirmatory test show positive results (Communicable Disease Management Protocol., 2010).

Repeat screening of high risk women is indicated in the third trimester even if an earlier screen was negative for HIV (Communicable Disease Management Protocol., 2010).

1.3.2.3 Treatment and prevention of HIV infection

The treatment of HIV infection depends mainly on several factors including HIV viral load, CD4 lymphocyte count, clinical stage of disease and patient motivation to start and remain on therapy (CDC, 2009). The goal of therapy in HIV is to reduce circulating HIV virus levels, optimize the patient's immune system and minimize risk of complications related to HIV infection including opportunistic infections (CDC., 2009). Highly active antiretroviral therapy (HAART) is considered the principal method for treating HIV infection (Masia *et al*., 2013). When opportunistic infections present, treatment is indicated (Masia *et al*., 2013). In addition, there is evidence suggesting that non-AIDS-defining illnesses, specifically psychiatric and renal disease may also be reduced by HAART administration (Masia *et al*., 2013). Nevertheless, not all non-AIDS-defining illnesses improve when HAART is administered, such as liver and cardiovascular disease (Masia *et al*., 2013). Although pregnancy does not affect or influence the progression of HIV infection, prenatal screening of HIV infection is highly recommended to enable use of interventions to prevent transmission of HIV (Watts., 2002 and Minkoff *et al*., 2003).

1.3.2.4 Prenatal screening for HIV infection

Testing pregnant women for HIV infection is recommended and offered routinely in different parts of the world (Newell and Thorne., 1997, Noone, Goldberg., 1997 and McGowan and Shah., 2000). Lewis *et al.,* 1995 indicated that prenatal screening programs have significantly contributed to a reduction of congenital HIV cases. Prenatal testing allows the health care provider to initiate timely ART in combination with avoidance of breastfeeding or Caesarean section to avoid MTCT of infection (Chou *et al*., 2005). A Canadian study estimates that 65% of vertically transmitted cases would be eliminated if prenatal screening for HIV was applied to 90% of pregnant women (Archibald et al., 1999 and Health Canada., 2001). Manitoban pregnant women are routinely offered screening for HIV at their first prenatal visit. Nevertheless, there are still a number of women who opt out of the test. While the reasons that Manitoba women opt out are not known, studies in other jurisdictions indicate women opt out due to numerous religious and social reasons such as the fear of discrimination, denial of a positive diagnosis and stigmatization (Turan *et al*., 2011).

1.3.3 HBV infection

HBV, which primarily infects hepatocytes, is a small enveloped double stranded DNA virus belonging to the Hepadnaviridae family (Conly and Johnston., 2007 and Koziel and Siddiqui., 2010). Four major subtypes of HBV are recognized (adw, ayw, adr and ayr) based on antibody response to HBsAg

(Heymann., 2008). The distribution of these subtypes varies geographically (Heymann., 2008). However, no subtype-related differences in clinical presentation have been reported (Heymann., 2008). Studies have suggested that there are eight genotypes (A-H) which can play an important role in disease progression from acute to chronic infection (Heymann., 2008, Conly and Johnston., 2007). Researchers have reported that genotype A is the most commonly observed in northern Europe and North America, (Heymann., 2008, Conly and Johnston., 2007, Lok and McMahon., 2007 and Chen *et al*., 2007).

The virus is transmitted mainly through sexual contact with an infected person, transfusion of an infected blood component or from an infected mother to her baby during delivery (Ganem and Schneider., 2001). Prenatal transmission of HBV has not reported due to the virus size which cannot cross the placenta (Mahoney *et al*., 1999). Due to the possibility of MTCT, prenatal screening is recommended to detect mothers with HBV and prevent MTCT infection accordingly (Hollinger and Liang., 2001).

1.3.3.1 HBV epidemiology

HBV is endemic worldwide with approximately two billion infected people (Heymann., 2008 and Pungpapong *et al*, 2007). From these infected people, approximately 350 million are chronically infected with HBV worldwide (Heymann., 2008). In the Far East, the Middle East, Africa, South America, Eastern Europe and Central Asia, hepatitis B infection remains highly or moderately endemic with carrier rates of 2% to 20%. On the other hand, low

endemicity is found in the United States, Western Europe, and Australia (Heymann., 2008). In most of Africa and Asia, chronic HBV infection is common and usually acquired prenatally or in childhood (Lavanchy., 2004).

In Canada, statistical studies show that 300,000 people are infected with HBV (Canadian Liver Foundation., 2012). The vast majority of these HBV carrier cases are immigrants from endemic countries (PHAC., 2013). Due to the wide use of vaccination, the incidence rate of HBV has significantly decreased in all age groups in Canada (Sherman *et al*., 2007).

In 2011, 245 new cases of hepatitis B were reported in Manitoba. Of these, six were acute cases, while the others were characterized as either chronic or unspecified infection. Eighty three percent of hepatitis B cases reported in Manitoba were residents in the Winnipeg Health Region. The crude rate of reported HBV cases increased between 2002 and 2011. The number of reported hepatitis B acute cases during this period has varied between two and twelve cases per year (Communicable Disease Management Protocol., 2013).

1.3.3.2 Laboratory diagnosis of HBV at CPL

Assessment of liver function is the first non-specific diagnostic method of hepatitis infections (Hollinger and Liang., 2001). The presence of high alanine aminotransferase (ALT) is the hallmark of hepatitis infections (Hollinger and Liang., 2001).

The diagnosis of acute infection is based on the detection of both HBsAg and anti-HBc IgM. HBsAg can be detected several days to several weeks before

the presence of symptoms and remains weeks or months after in acute cases (Hollinger and Liang., 2001). When HBsAg starts to decline and then disappears, anti- HBs starts to appear which is considered an indication of the acute phase of the infection (Hollinger and Liang., 2001). Anti-HBc IgM is present in high titer in acute cases and usually disappears within six months (Hollinger and Liang., 2001).

The diagnosis of chronic cases is typically based on the persistence of HBsAg for more than six months. The presence of HBsAg and anti-HBc total antibody, in the absence of anti-HBc IgM is also diagnostic of chronic cases of hepatitis B infection (Communicable Disease Management Protocol., 2013).

1.3.3.3 Treatment and prevention of HBV infection

Supportive treatments are used in acute HBV cases (Shiffman., 2010). In chronic cases, treatments are used to prevent liver failure, cirrhosis and hepatocellular carcinoma (Sherman *et al*., 2007).

Several strategies have been suggested to prevent hepatitis B infection such as blood donor screening, prenatal screening and HBV immunization (Hollinger and Liang., 2001). Vaccination against HBV is considered an effective way to prevent the consequences of acute and chronic HBV infection (WHO., 2013).

1.3.3.4 Prenatal screening of HBV

Prenatal screening of HBV is critically important to prevent or minimize MTCTof the infection (U.S. Preventive Services Task Force [USPSTF], 2010). Due to the presence of a highly effective vaccine and HBV specific immunoglobulin, all pregnant women presenting for prenatal care are recommended to be tested for the presence of HBsAg early in their pregnancy (American College of Obstetricians and Gynecologists (ACOG)., 2007). It has been shown that early detection and identification of infected women considerably decreases the chance of virus transmission to their newborn and prevents subsequent risk of chronic HBV consequences (USPSTF., 2010). Timely screening followed by appropriate care and interventions are the key that provide an effective prevention strategy against HBV transmission (USPSTF., 2010). Women who have positive HBsAg are considered infectious and their newborns should be immediately immunized, and HBV immunoglobulin should be administered after birth to stop MTCT (Mahoney.,1999).

1.4 Bacterial Infections

Bacterial infections during pregnancy can have a major negative impact on women and their fetuses (Goldenberg *et al*., 2005). It can affect pregnant women at any stage of pregnancy from attachment of the fertilized ovum to the time of delivery. It has been revealed that different types of bacterial infections can be transmitted to the fetus and affect the newborn (Blas *et al*., 2007). Syphilis, Ct and GC are examples of bacterial infections that may lead to

stillbirth, spontaneous abortion or death in untreated women (Liu *et al*., 2013 and Stokes *et al*., 1945). Although preventative measures and treatments are available for these infections, they still cause significant health concerns in Canada (PHAC., 2012a). Since the 1990s, the rate of people Infected with syphilis, CT and GC showed a steady increase among Canadians (PHAC., 2013). In general, many women with these infections are asymptomatic, needing both a high degree of clinical suspicion and adequate screening during pregnancy to receive necessary treatment and care and therefore, prevent MTCT of bacterial infections.

1.4.1 Syphilis infection

Treponema pallidum is the cause of syphilis infection (Berman., 2004). It belongs to Spirochaeraceae family (Sung and MacDonald., 1998). Serological detection of the infection remains the main method for syphilis diagnosis (Ratnam., 2005). Untreated patients with syphilis infection progress through three well-recognized and characteristic stages (primary, secondary, and tertiary) (Ratnam., 2005). The last stage may have several complications that might be similar to complications observed in other diseases (Ratnam., 2005).

The main routes for syphilis transmission in children are sexual abuse or transplacentally from infected mothers to their fetuses which are described as acquired syphilis and congenital syphilis, respectively (Fiumara 1995, Tsui *et al*,

1997, Wolff *et al*., 2009). Other modes of transmission have been identified such as contact with infected tissues or contaminated blood (Wolff *et al*., 2009).

In mothers with primary or secondary untreated syphilis, the transmission rate of syphilis infection is very high and can reach 100% compared to 30% in mothers with late syphilis infection (Harter and Benirschke., 1976). Manifestations are described as either early or late if they appear in the infected neonates before or after two years of age, respectively (Gupta and Vora., 2013). It has been shown that early untreated syphilis infection may lead to a number of serious complications such as deafness, neurologic impairment, bone deformities, and neonatal death (LaFond and Lukehart., 2006). Consideration of early prenatal screening for syphilis infection can significantly reduce the risk of MTCT (Hammerschlag., 2011 and Darling., 2009).

1.4.1.1 Syphilis epidemiology

According to CDC statistics, 55,400 people get infected with syphilis each year In the U.S. In 2011, 46,042 new syphilis cases were reported (CDC, 2013) with 360 congenital syphilis infection cases being reported in the same time period (CDC, 2012b). Overall, a decrease in MTCT syphilis infection rates among newborns in the U.S. has been recognized in the last few years (CDC., 2012b). Also, syphilis is a serious health problem in developing countries (WHO., 2013). It is believed that antenatal screening and treatment of infected mothers plays a

significant role in controlling the infection and reducing the risk of transmission (Wolff *et al*., 2009).

In Canada, the incidence rate of contagious syphilis was low in the 1990s. However, the rate has increased from 0.4-0.6/100,000 between 1994 and 2000 to 3.5/100,000 in 2004 (PHAC, 2007). The number of the new cases reported in 2008 was 1,394 cases (PHAC., 2010b). Although some increase in the rate of MTCT syphilis infection has been noted recently, the overall rate is considered very low compared to previous years (PHAC., 2010b).

In Manitoba, a locally acquired Syphilis outbreak occurred in 2003 with risk factors determined to be unprotected sex, men who have sex with men (MSM), and heavy alcohol use (Manitoba Health., 2005). Most incidents of syphilis infection were reported among residents in Winnipeg (Manitoba Health., 2005). Men 40-44 years of age and females between 30- 34 years of age were the main age groups subject to infection (Manitoba Health., 2005).

1.4.1.2 Laboratory diagnosis of syphilis infection at CPL

In CPL, specific and non-specific serology tests for syphilis are performed. They are important for screening and diagnostic purposes in addition to monitoring of the infection. Specific treponemal diagnostic tests include *Treponema. pallidum* practical agglutination test (TP-PA) and fluorescence treponemal antibody absorption test (FTA-ABS). TP-PA detects antibodies raised

against several subspecies of *Treponema pallidum*, and is considered a confirmatory test at CPL (Communicable Disease Management Protocol, 2007).

1.4.1.3 Treatment and prevention of syphilis infection

In all three stages of the disease, penicillin is used to treat syphilis infection (David *et al*., 2011). Excellent patient prognosis has been observed when both adequate and timely treatment was provided (David *et al*., 2011). Avoiding unprotected sex and undertaking prenatal testing in each pregnancy reduce the risk of syphilis infection (Farley *et al*., 2000).

1.4.2 CT infection

CT is a bacterial infection caused by *Chlamydia trachomatis* (Somani *et al*., 2000). It is the most commonly reported bacterial STI worldwide (Clad *et al*., 2001). Although the majority of infected women are asymptomatic, some of them develop pelvic inflammatory disease (PID) (Weir., 2004, Geisler William, 2004). Further complications such as chronic PID, infertility, and ectopic pregnancy are also associated with CT infection (Hu *et al*., 2004). It is believed that direct sexual contact as well as congenital transmission to a child is the main routes of transmission (Weir *et al*., 2004, Jacobson *et al*., 2001). MTCT of CT infection is usually associated with conjunctivitis and pneumonia in newborns (Somani *et al*.,

2000). Thus, early detection of CT infection during pregnancy can prevent these complications (Hammerschlag., 2011).

1.4.2.1 CT epidemiology

According to the WHO, more than one million people become infected with STIs (e.g, CT, GC, syphilis) daily (WHO., 2013). It was estimated that approximately 89 million people worldwide were infected with CT in 1995 (Clad *et al*., 2001). The highest incidence rate was reported in Asia and sub-Saharan Africa (PHAC., 2003). Women of reproductive age have the highest rate of reported CT infection in the U.S. (Robert *et al*., 2011).

In Canada, although CT infection is asymptomatic in many cases, it is the most common reported infection (PHAC., 2010). Prevalence studies indicate that the number of genital CT infections has been increasing since 1997 (Weir *et al*., 2004 and PHAC., 2012a). The incidence rate was estimated to be 197/100000 population in 2004 with the highest prevalence in females and males aged 20-24 years (PHAC., 2007). Between 2001 and 2010, an estimated increase of 72% in reported cases was observed inclusive of both males and females (PHAC., 2012a). The number of CT infection cases reported in 2010 was 94,690 with most of these cases identified in young women between 20-24 years old (PHAC., 2012a)

In Manitoba, the rate of CT cases was 275/100000 population in 1998 (Elliott *et al*., 2002). The rate of the infection between 1996 and 2004 increased

from 222 to 363 per 100000 populations, respectively (Beaudoin., 2006). The highest number of reported cases was observed in women between 15- 24 years old (Beaudoin., 2006).

1.4.2.2 Treatment and prevention of CT infection

In pregnant women, azithromycin is considered the first effective and safe option to use in urogenital CT infection cases (Pitsouni *et al*., 2007). Other treatments such as amoxicillin and erythromycin are used as alternatives (Pitsouni *et al*., 2007). Avoiding unprotected sex is also considered important to reduce the risk of CT transmission (Weir *et al*., 2004, Jacobson *et al*., 2001).

1.4.3 GC infection

GC infection is the second most commonly reported bacterial STD in Canada (PHAC, 2012a). It is caused by *Neisseria gonorrhea* (Genco and Wetzler, 2010). Although about 50% of infected pregnant women are asymptomatic, serious complications such as ectopic pregnancy, infertility, endocervicitis, bacteremia, and intrauterine growth retardation have been reported (Hollier & Workowski., 2005).

Transplacental transmission of *GC* is not well documented (Brocklehurst., 2009). Rather, congenital transmission during vaginal delivery is believed to be the main mode for MTCT of GC infection (Brocklehurst., 2009). Newborns who

acquire the infection during the birth process may develop numerous manifestations including acute conjunctivitis, sepsis, blindness and meningitis (Brocklehurst., 2009). Early detection of the infection in addition to receiving appropriate and adequate treatment can dramatically reduce or completely prevent the complication of GC infection (Hammerschlag., 2011 and USPSTF., 2005).

1.4.3.1 GC epidemiology

GC infection is most prevalent in developing countries and both males and females are at risk of acquiring the infection. Following Ct, GC infection is the second most reported STI in the U.S. (Walker and Sweet., 2011). As estimated by the CDC, more than 700,000 new cases occur in the U.S. annually (CDC., 2009).

In Canada, the rate of GC infection has been increasing since the 1990s with the highest rates reported in Yukon, Northwest Territories, and Nunavut (PHAC., 2012a and Law *et al.,* 2008). From 2001 to 2010, an increase of 53% in the number of reported cases was observed (PHAC., 2012a). Over the same period of time, screening and identification measures have improved considerably which in turn affect the rate of reported cases (PHAC., 2012a). Among young females aged between 15 and 19 years old, 147/100,000 new cases were reported in 2010 (PHAC., 2012a).

In Manitoba, the rate of GC infection in 2004 was drastically higher (93/100000 populations) than the national average (29/100000 populations)

(PHAC., 2007 and Communicable Disease Management Protocol., 2008). The rate further increased to 100 and 134 per 100000 populations in 2005 and 2006, respectively (Communicable Disease Management Protocol., 2008). More than half of the cases reported between 2003 and 2006 were among residents of Winnipeg (Communicable Disease Management Protocol., 2008).

1.4.3.2 Treatment and prevention of GC infection

Identification and treatment of infected women is essential to eliminate the transmission of GC infection (Darling., 2009). In addition to GC, PID can be caused by other pathogens such as CT, streptococci and gram negative bacteria. Therefore, a combination of three antibiotics is recommended (Ceftriaxone, Doxycycline, and Metronidazole) to treat PID cases (Communicable Disease Management Protocol., 2008). Timely treatment is critical to prevent long term complications associated with the infection (Brocklehurst., 2009). Hence, treatment should be administrated as soon as a GC case is confirmed. As a prevention step, prenatal screening is essential to identify infected women and prevent MTCT (Darling., 2009 and USPSTF., 2005).

1.4.3.3 Laboratory diagnosis of CT and GC at CPL

Due to its sensitivity, an endocervical swab is the most recommended specimen to diagnose both CT and GC infection for women. Urine (first 20 to 30

ml of urine) is a second available option for women and the preferred option for men. Gen-Probe Aptima technology is a NAAT used for diagnosis of GC and CT from urine and swab specimens submitted to CPL. CPL also provides a Gen-Probe Aptima specimen collection kit that is necessary for specimen transportation and NAAT. In the case of a suspected GC infection in newborns, culture is strongly recommended although NAAT is also considered diagnostic (Communicable Disease Management Protocol., 2008).

1.4.4 Prenatal screening of bacterial STIs

Several preventive strategies have been suggested to reduce the risk of STI transmission. Performing prenatal screening early and in each pregnancy is critical in preventing the morbidity of neonatal infection and improving the pregnancy outcome (Hammerschlag., 2011 and Darling., 2009). Indeed, CT and GC prenatal screening should be offered to all pregnant women at the first prenatal visit because infected women are often asymptomatic (Majeroni et al., 2007). It is recommended that pregnant woman younger than 25 years and high-risk patients (e.g., women with multiple partners) who tested negative in the first trimester undergo screening again in the third trimester (CDC., 2010).

1.5 Rationale, hypothesis and objectives of this study

Infections during pregnancy can pose a substantial risk for the pregnant women, fetus and newborn if left untreated (Schmidt *et al*., 2009). For several

infectious agents, prenatal screening and safe and effective medical interventions exist to minimize the risk of MTCT and subsequent congenital infections. Pathogens, such as HIV, syphilis, HBV, rubella, CT and GC are examples of infections for which medical interventions are available. Initiation of treatment for these infections is dependent on effective screening during pregnancy.

Several studies have been conducted to assess the effectiveness of prenatal screening programs in preventing infections. In The Netherlands, antenatal screening has been found to prevent approximately, 10 syphilis, 5 -10 HIV, and 50 - 75 HBV cases in infants each year (Op de Coul *et al*., 2011). Many findings have also provided strong evidence to support the importance of screening pregnant women for CT to avert MTCT infections (Cohen *et al*., 1990 and Haddix *et al*., 1995).

Despite the clear importance of prenatal screening, it is known that many pregnant women do not undergo screening during pregnancy or they receive an incomplete set of screening tests. For example, 12% of pregnant women missed a screening test for syphilis infection in Switzerland (Frischknecht *et al*., 2011) and data from Brazil revealed that screening for HIV and syphilis is missed in 56% and 41.2% of pregnancies, respectively (Rodrigues *et al*., 2008). The testing rate for HIV in India was found to follow the same trend with only 45% of pregnant women screened for HIV infection (Reilley *et al*., 2011). In addition, 33% of pregnant women were not screened for HIV infection in Switzerland and only 73.82% are screened for HIV in California (Frischknecht *et al*., 2011 and

Sheikh *et al*., 2009). Similar findings have been observed in Germany (Frischknecht *et al*., 2011).

Given these findings, it is extremely important to assess the extent to which pregnant women in Manitoba are screened for GC, CT, HBV, syphilis, HIV and rubella. An assessment of this kind will determine whether low or incomplete rates of screening are occurring in this province. **The hypothesis tested in this thesis is that prenatal testing for GC, CT, HBV, syphilis, HIV and rubella is suboptimal when compared to the number of live births and stillbirth (as a surrogate of all pregnancies) occurring in Manitoba.** The purpose of this study is to determine the rates of prenatal screening, link this data to demographic information and determine what factors contribute to suboptimal prenatal STI testing rates. These results can be used to more effectively design and deliver education to ordering practitioners to optimize PMTCT strategies and reduce congenital infections. The study objectives include:

1. Determine the proportion of pregnant women who did not receive the entire prenatal screening panel over the six year time period of the study from January 2006 to December 2011 (the entire panel is considered to consist of screening for syphilis, rubella, HBsAg and HIV in addition to GC, and CT),.
2. Identify the change in adherence to the prenatal screening program over the six year period from January 2006 to December 2011.

3. Determine the percentage of screened women who did not receive screening tests for some of the infections in each year from from January 2006 to December 2011.
4. Assess the effectiveness of the prenatal screening program in preventing potential MTCT infections during the period from January 2009 to December 2011.
5. Determine the relationship between age, area of residence and the rate of women receiving prenatal screening from from January 2006 to December 2011.

2. Methodology

2.1 Study Time Frame and Study Population

The analysis of this study was performed using data from a six-year period from January 1, 2006 to December 31, 2011. The study population consisted of pregnant women residing in Manitoba who had received prenatal screening for each of HBV, HIV, rubella, syphilis, CT and GC performed at CPL.

2.2 Ethical Considerations

Ethics approval for data collection and analysis for this proposal was obtained from the Health Research Ethics Board (HREB) and the Health Information Privacy Committee (HIPC) at the University of Manitoba and Manitoba Health, respectively, prior to the start of data extraction. The original HREB and HIPC approval letters can be found in Appendix A and B.

2.3 Data Source and Collection Site

Prenatal testing and demographic data for the six-year period from January 2006 to December 2011 was collected from CPL databases. CPL, which is the Manitoba provincial health laboratory, has been responsible for providing the public with clinical laboratory services in Manitoba since 1897. The data was provided in aggregated form by Roy Cole, the Laboratory Liaison Technical Officer (LLTO) at CPL. In addition, the annual total number of pregnancies, as estimated by total live and still births in the province reported in Manitoba

between 2006 and 2011, was obtained from Vital Statistical Agency (VSA) ANNUAL REPORT 2011/2012.

2.4 Study Design

In order to achieve the objectives outlined, this retrospective cohort study reviewed and analyzed prenatal data collected from CPL databases. This study used data from Manitoban pregnant women who received prenatal screening tests for potential infectious diseases: HIV, HBV, rubella, syphilis, CT and GC during the study period between January 1, 2006 and December 31, 2011. Only aggregated data consisting of specific information and variables for pregnant women in Manitoba over the study period was used for this study. As noted below the original data extracts did contain information including personal health information numbers (PHINs), however, this data was only used by the LLTO for purposes of data manipulation. The aggregated data provided to the student for this study did not contain PHINs or any other personal identifiers. Aggregated data was prepared by the LLTO and obtained directly from him.

2.5 Data Extraction

Prenatal data from 76288 Manitoban pregnant women from January 2006 to December 2011 was extracted from two CPL databases:

1- Mainframe database which provides prenatal data from 2006 to 2009.

2- LabWare Laboratory Information Management System (LIMS) database which provides prenatal data from 2009 up to the current date.

From both Mainframe and LIMS databases, prenatal information was extracted and segregated according to distinct PHIN codes for each patient. Any duplicate PHIN codes in the same year were removed so that each pregnant woman was counted only one time. In addition, all pregnant women from out of Manitoba were excluded from the analysis, to ensure the study data reflected Manitoba-specific trends. In Excel files, relevant information was separated according to the variables assigned for this study.

2.5.1 Prenatal Data Extraction from 2006 to 2009.

Prenatal information from 2006 to 2009 was extracted and collected from the Mainframe database at CPL. this database is maintained and the queries executed by the Information Systems Branch (ISB) at Manitoba Health. This query made a line list of all prenatal samples and each test was represented by a distinct line on an Access database. The database was queried to separate the samples into each distinct test for each infection (HBV, HIV, rubella, syphilis, CT and GC) by year and the data elements included sample ID, PHIN, test code, test result, patient age, clinic, physician, and patient address. Data was then aggregated and transferred to Excel file sheets and provided to the researcher for analysis.

2.5.2 Prenatal Data Extraction form 2009 to 2011.

The prenatal data from 2009 to 2011 was extracted from the current LIMS Labware database at CPL. For each test; annual samples were collected into a

line list by year of sample received. The same data elements (sample ID, PHIN, test code, test result, patient age, clinic, physician, and patient address) that were extracted from the Mainframe database were extracted from the LIMS database. The prenatal samples were separated from the overall annual list and were then organized into an Excel file according to test types and provided to the researcher as aggregate data in order to perform the data analysis.

As noted above, to ensure patient confidentiality, no direct identifiers appeared in the aggregated data.

2.6 Data Confidentiality

Aggregate data specifically for HIV, HBV, rubella, syphilis, CT and GC was maintained at CPL, a secure governmental lab in Manitoba. Access to the laboratory is restricted by automatically locked doors that require card access to restricted areas. Access to study data was only performed on-site at CPL on computers that are password and username protected. Approval by the HREB and the HIPC had been obtained to extract the data and do the analysis. The proposed protocol was based on using aggregate information from Manitoban pregnant women so there were no specific identifiers included. In addition, accessing and analysis of patient information was limited to the investigator and supervisors. Only the LLTO had access to data with PHINs. The investigator and her supervisors were provided only with aggregated data that did not contain PHINs or any personal identifier. Finally, to ensure maximum security, storing or

copying to any other device and emailing any information to other person was totally prohibited.

2.7 Demographic Data

For this study, the interest was to characterize the adherence with prenatal screening recommendations for infectious diseases in Manitoba and identifying any associations between prenatal screening and demographic variables over the time period from January 2006 to December 2011. Data on age, area of residence, tests results for pregnant women as well as test results of HBV, HIV, rubella, syphilis, CT and GC in newborns were included in the study.

To assess the relationship between receiving prenatal screening tests and the age of pregnant women, five age groups: (<15, 15-25, 26-35, 36-45 and 45+ years old) were identified according to the age of a woman at the time of pregnancy.

Based on the first three digits of a postal code, the association between area of residence and receipt of prenatal screening for each infection was determined. Pregnant women who received at least one of the prenatal screening tests were divided into three groups. These groups corresponded to the two largest urban areas within Manitoba, Winnipeg and Brandon, with all remaining areas grouped together (designated as “rural” for this thesis).

Results of prenatal screening tests for each infection were extracted and categorized as positive results, negative results and undetermined. Results that were labelled as undetermined was excluded from analysis. Infants diagnosed

with HIV, HBV, syphilis, rubella, CT or GC during the first year of life were reported as positive results and considered congenitally infected. Data was then aggregated according to the above mentioned factors for each infection and separated in Excel files for statistical analysis. Figure 1 shows a summary of Study design and objectives.

2.8 Proportion of Manitoban pregnant women who received prenatal screening tests for (HBV, HIV, rubella, syphilis, CT and GC) over six-year period from 2006 to 2011.

Total number of births (live births and stillbirths) reported over the six year period (n= 96,233 births) was used as an estimated number of total pregnancies in Manitoba. Stillbirths in this study were defined as fetuses that died at 20 or more gestation weeks or those weighing 500 gram or more at death. Total number of prenatal requisition forms received over the six year period (n=76288) was used to determine the total number of screened pregnant women. In this study, screened pregnant women were identified as women who received a prenatal screening test for at least one of the infections of interest: (HBV, HIV, rubella, syphilis, CT and GC). Of note, any duplicate PHIN codes in the same year were removed so that each pregnant woman was counted only one time.

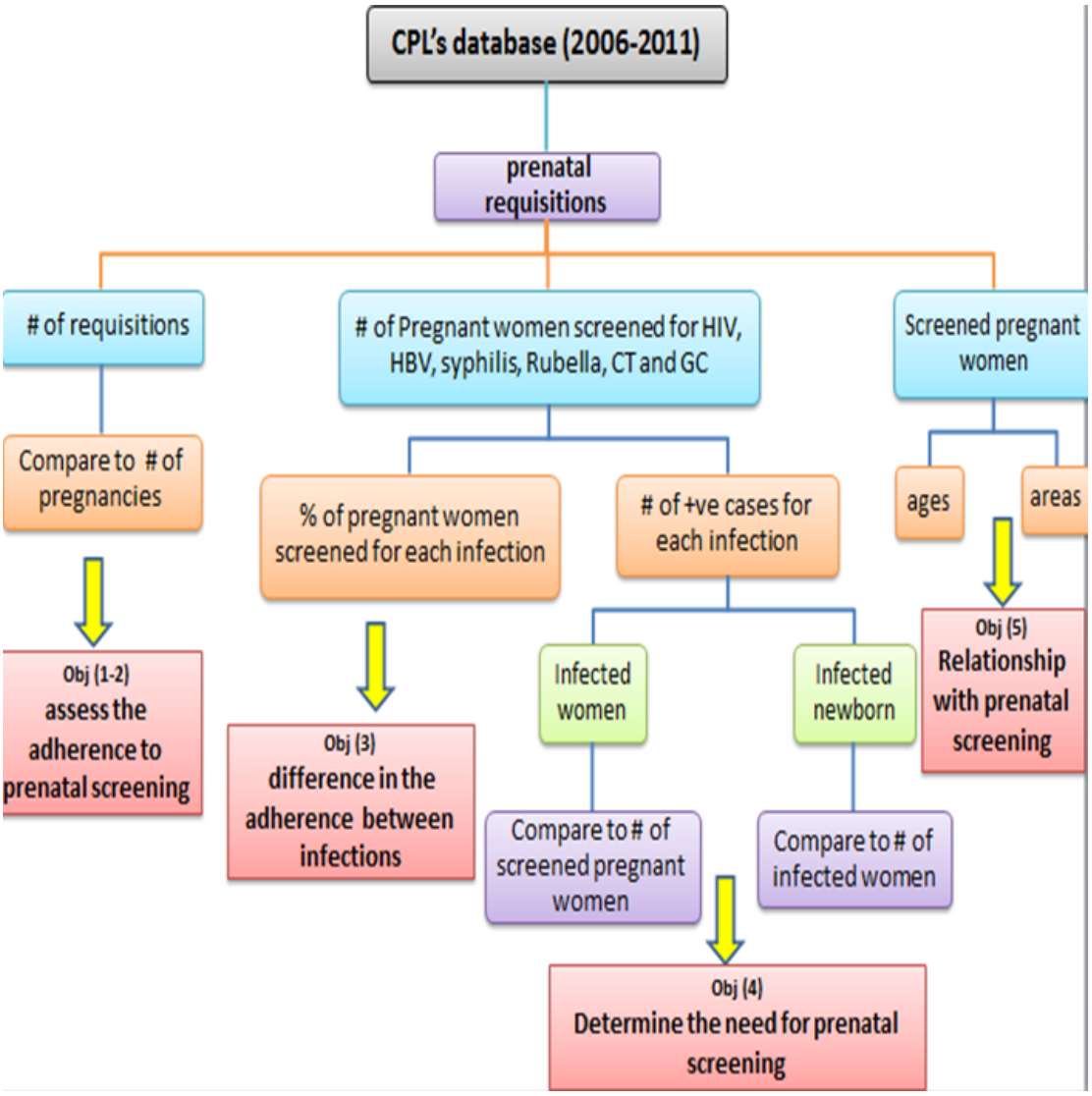


Figure 1: Study design and objectives

To assess the overall adherence to prenatal screening guidelines for infectious diseases between 2006 and 2011 in Manitoba, the proportion (%) of screened women to total number of births was determined.

2.9 Annual adherence to prenatal screening recommendations for (HBV, HIV, rubella, syphilis, CT and GC) infections in Manitoba from 2006 to 2011.

While the analysis above cumulatively examined the proportion of women screened over the entire six year study period, a more detailed breakdown of results was undertaken by examining the annual adherence to prenatal screening recommendations for infectious diseases. This analysis was done in order to identify whether there is any change from year to year in prenatal screening rates. For all six years, the proportion (%) of screened women in a given year to total number of births reported in that particular year was determined.

2.10 Adherence to prenatal screening recommendations for each infection (HIV, HBV, rubella, syphilis, CT and GC) over the six year period.

The adherence to prenatal screening regulations for each infection was assessed in order to identify any noticeable discrepancy in requesting a given test in comparison with the others during study period. Relative to the total number of births, the proportion (%) of those pregnancies had been tested for each individual pathogen (HIV, HBV, rubella, syphilis, CT and GC) over the six year period was determined.

2.11 Changes in the annual adherence to prenatal screening recommendations of each infection (HIV, HBV, rubella, syphilis, CT and GC).

During the study period, two requisition forms were in use at CPL. One of the differences between these forms could potentially have an impact on prenatal testing, therefore, this analysis was undertaken to better understand whether any transitional periods in screening were evident in the data. From 2006 to June 2008, the requisition in use contained no panels or tick-off boxes and instead medical practitioners were requested to write down each test that they required. Since June 2008, the requisition form in use includes a tick-off box for a prenatal panel. This panel consists of testing for HBV, HIV, rubella and syphilis (a patient does have the option of opting out of the HIV portion of this panel). A second tick-off box includes both of CT and GC.

In order to identify any change in the adherence to any of the prenatal screening tests, the annual adherence to screening for each infection of interest was assessed, and the trend of testing over the six-year period of the study was followed. Annual total numbers of screening tests for each infection from 2006 to 2011 were calculated, and calculated as a proportion (%) relative to the number of births reported in each year.

2.12 Effectiveness of prenatal screening program in identifying infected pregnant women and preventing MTCT infections in newborn.

The effectiveness of following prenatal screening recommendations for HIV, HBV, rubella, syphilis, CT and GC in detecting infected pregnant women

was evaluated. The annual number of pregnant women who received prenatal screening tests for any of the infections included in the study and who were subsequently identified as positive for HIV, HBV, syphilis, CT and GC, or reported as IgG negative to rubella infection were identified. Annual rates were calculated from this data.

In addition, the effectiveness of the prenatal screening program in preventing potential MTCT of HIV, HBV and syphilis among infants born from 2009 – 2011 was determined. Due to the presence of undetermined tests results, years from 2006 – 2008 and the other infections were excluded in this part of study. Information on pregnant women infected with HBV and syphilis between 2006 and 2008 was unavailable. Also, the number of pregnant HIV-infected mothers in 2008 was not available. The number of MTCT of HBV, syphilis, and rubella cases between 2006 and 2008 were missing. The presence of any of these infections during the first year of life of infants was considered as a MTCT infection.

It has been reported in 2011 by Op de Coul *et al.* that the average risk of MTCT is 20-30% for HIV/ HBV, and 50% for syphilis (Op de Coul *et al*., 2011). The estimated percentage of MTCT infections potentially averted due to the use of prenatal screening was calculated based on these estimated risks in conjunction with the number of pregnant women confirmed positive for HIV, HBV or syphilis.

2.13 Association between demographic factors (age and area of residence) and the receipt of a prenatal screening test from 2006 to 2011.

Screened pregnant women were divided according to age into five age groups: <15, 15-25, 26-35, 36-45 and 45+ years old. The total number of pregnant women receiving prenatal screening tests for each of HIV, HBV, rubella, syphilis, CT and GC within each age group was calculated as a proportion relative to the total number of requisition forms within that age group.

Associations between geographic area of residence and screening were assessed using the first three digits of the postal code for each screened woman at the time of a given pregnancy. As noted above, area of residence was divided into three areas: Winnipeg, Brandon and rural. Since Winnipeg and Brandon are the largest and most populated cities in the province, any postal codes outside of Winnipeg and Brandon were considered as rural areas.

To identify any associations between geographic area and adherence with the prenatal screening program, the total number of tests for each infection of HIV, HBV, rubella, syphilis, CT and GC over the six year period of the study in each area was calculated as a proportion relative to the total number of screened pregnancies within the same area.

2.14 Statistical Analysis

Proportions (%) and 95% confidence intervals were determined for all analyses. Where applicable, significant differences between variables were

calculated by chi-square or chi-square test for trend. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were conducted using MedCalc software (Version 12.6.0, Acacialaan 22, B-8400 Ostend, Belgium).

3. Results:

3.1 Proportion of Manitoban pregnant women screened for infectious diseases.

A total of 96233 women gave birth in Manitoba during the study period. Within this population, there were 95,412 live births and 821 stillbirths. Table 1 below shows the annual number of births between 2006 and 2011. Of the 96233 Manitoban births reported, only 79.3 ± 0.3 % of them received at least one of the prenatal screening tests for the potential infectious diseases reviewed in this study. The rest of them had no documented prenatal records for the previously mentioned infections and were considered as unscreened pregnant women

3.2 The adherence to prenatal screening tests for potential infectious diseases.

The number of pregnant women (births) screened for at least one of the infectious diseases included in the study significantly decreased over the six year period. During each of the first three years of assessment, 83.7 ± 0.6%, 83.1± 0.6% and 82.6 ± 0.6% of births were prenatally screened for the included infections, respectively, but this decreased to 78.9 ± 0.6% in 2009 and 78.2 ± 0.6% in 2010. The screening rate noticeably declined further to 69.6± 0.7 % in 2011 ($p=0.019$) (Figure 2).

Years	Number of Pregnancies
2011	16334
2010	16393
2009	16504
2008	16058
2007	15816
2006	15128
Total	96233

Table 1: Annual number of Manitoban births between 2006 and 2011.

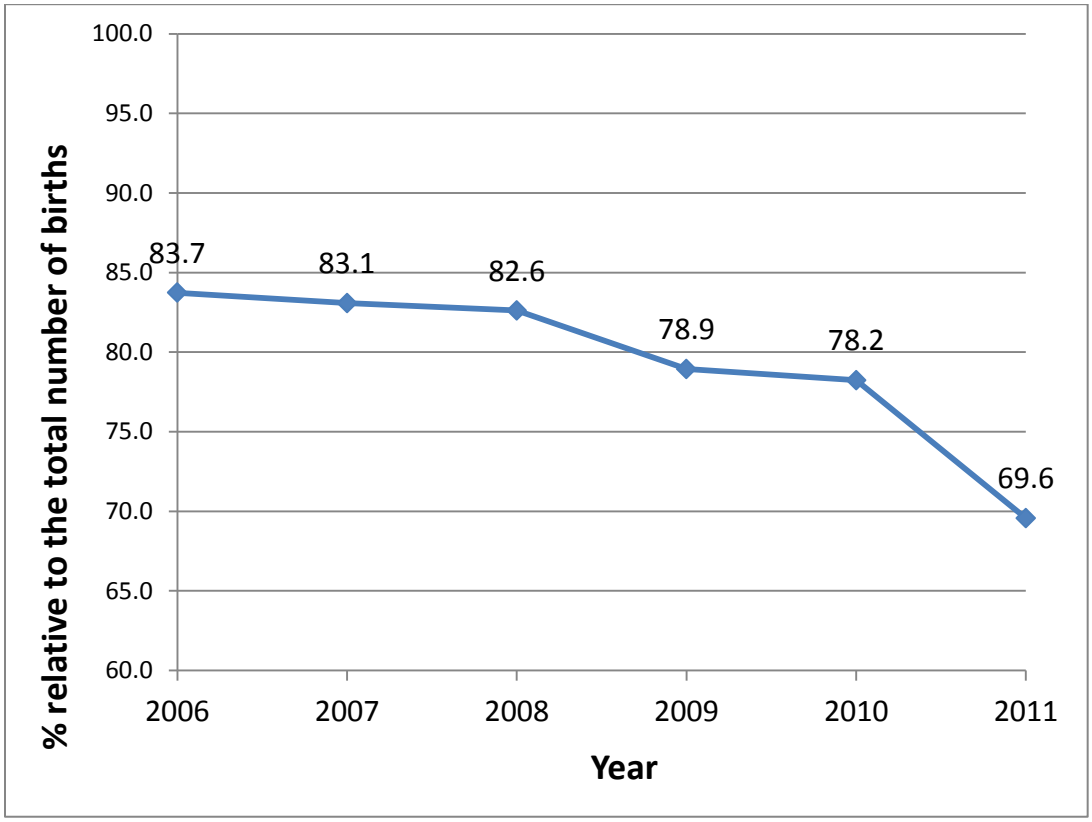


Figure 2: prenatal screening rates in MB from 2006 to 2011. Results are represented as percentages relative to the total number of births reported each year.

3.3 The annual adherence to overall prenatal screening tests for potential infectious diseases.

Over the six year period of the study, HBV, rubella, and syphilis screening tests were the most requested: 79.3 ± 0.3 % of the total number of Manitoban births. The rate of screening tests for HIV, CT and GC infections were significantly lower than HBV, rubella, and syphilis screening tests. For these latter tests, only 60.8 ± 0.3 % (p=0.005), 60.5 ± 0.3 % (p=0.005), and 57 ± 0.3 % (p=0.0008) of births received prenatal testing for HIV, Ct, and GC, respectively (Figure 3).

3.4 The annual adherence to prenatal screening recommendations of each infection (HIV, HBV, rubella, syphilis, CT and GC).

Prenatal testing for HIV infection showed a steady increase over the six year period of the study. Only 44.5 ± 0.8% of Manitoban births reported in 2006 received prenatal HIV screening tests. In 2011, this percentage increased to 65.9± 0.7% (p=0.0005). On the other hand, HBV, rubella, and syphilis screening tests were requested in 83.7± 0.6 % of births reported in 2006 followed by a significant decrease to 69.5± 0.7 % in 2011 (p=0.008).

The adherence to GC prenatal testing showed a slight statistically non-significant increase from 49.5 ± 0.8 % in 2006 to 54.3 ± 0.8% in 2011 (p=0.398). Prenatal CT screening tests remained stable over the six year period of the study with a slight decrease reported in 2011 (Figure 4).

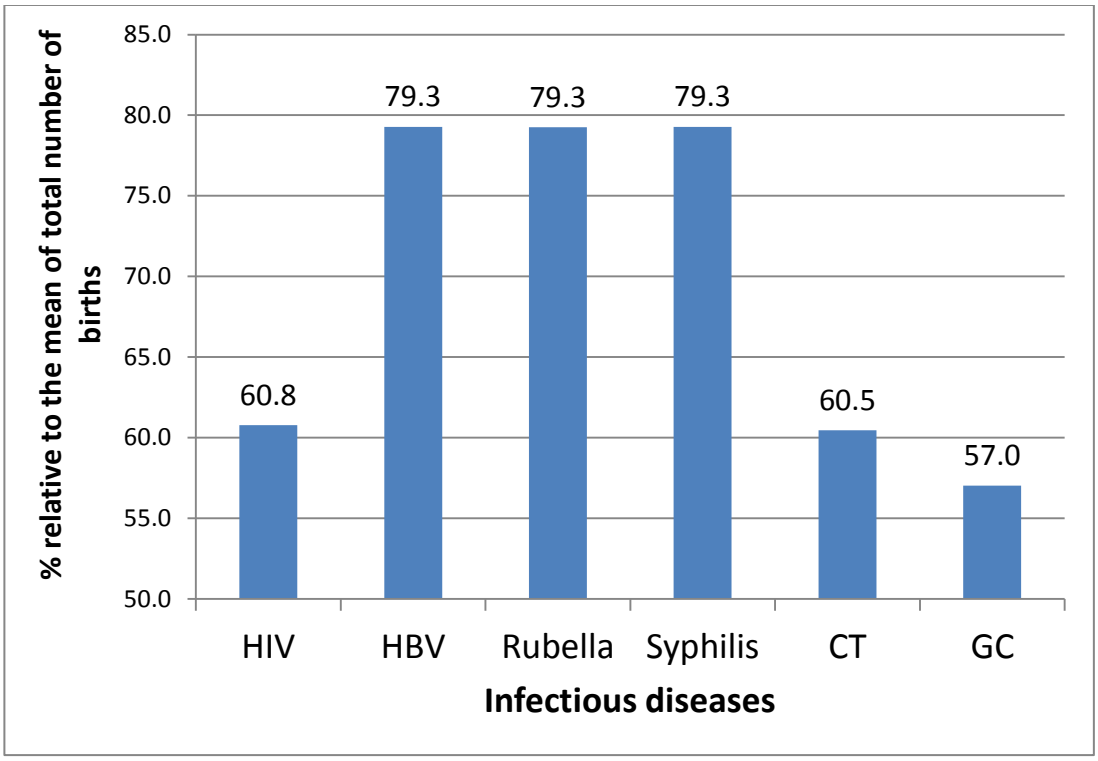


Figure 3: Adherence to screening each of the infectious diseases (HIV, HBV, Rubella, Syphilis, CT, and GC) over six-year period. Results are represented as percentages relative to the total number of births reported over six years.

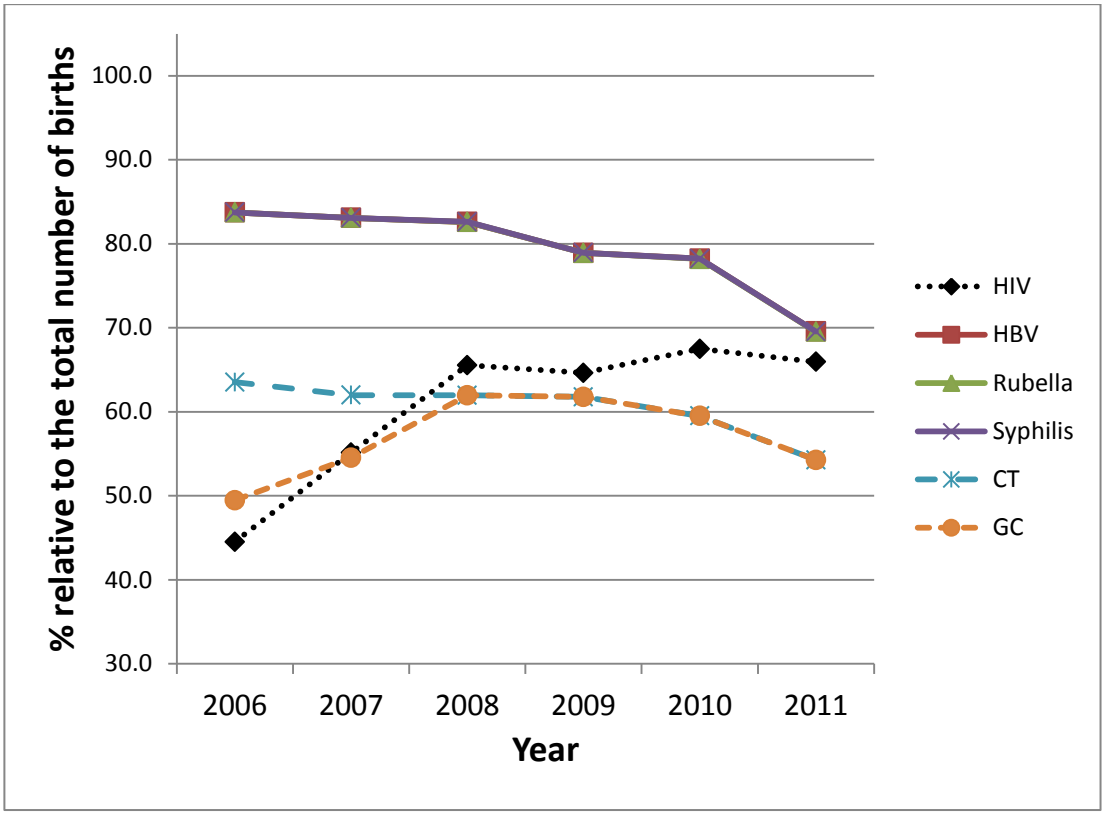


Figure 4: Change in adherence to each infection from 2006 to 2011. Results are represented as percentages relative to the total number of births reported each year.

3.4.1 The infection rate among screened pregnant women.

The positivity for each infection included in this project and the susceptibility for infection in case of rubella virus was evaluated in pregnant women who underwent prenatal screening. Results show that 1097 (1.1%) and 6314 (6.3%) out of 100,000 screened pregnant women were reported positive for GC and CT infections, respectively. Less frequently, 278 (0.28%) in every 100,000 pregnant women reported positive for HBV infection. Only 24.7 (0.03%) and 41 (0.04%) out of 100,000 pregnant women were reported positive for syphilis and HIV infections, respectively. The susceptibility to rubella infection was quite prevalent in this population of pregnant women. Analysis showed that 1 in every 10 pregnant women lack IgG for rubella infection (Table 2).

3.5 The estimated percentage of prevented HIV, syphilis and HBV MTCT infections among newborns between 2009 and 2011.

At first, it is important to indicate that due to the presence of undetermined tests results, years from 2006 – 2008 in the other infections were excluded in this part of the study as noted above. For instance, the numbers of pregnant women infected with HBV and syphilis and MTCT cases between 2006 and 2008 were unavailable. Also, the number of HIV-infected mothers in 2008 was missing.

Between 2009 and 2011, HIV, syphilis, and HBV infections were confirmed in 13, 9, and 102 pregnant women, respectively. Information on the receipt of prenatal screening tests or medical interventions for any of the infections was not available for these mothers. Only 1 case of HIV and 1 case of syphilis

Rates per 100,000 population							
	2006	2007	2008	2009	2010	2011	Overall
HIV	74.3	11.5	N/A	28.1	54.2	37.1	41
Syphilis	N/A	N/A	N/A	7.7	31.2	35.2	24.7
HBV	N/A	N/A	N/A	107.5	366.5	360.8	278.3
Rubella (IgG -ve)	12236.5	11316.6	10623.5	9498.6	8690.2	10963.4	10554.8
CT	3912.2	4906.2	7094.8	7218.5	7205.8	7547.4	6314.2
GC	988.8	1055	1004.9	1363.3	1086.5	1083	1096.9

Table 2: Rates of pregnant women infected with HIV, Syphilis, HBV, CT, and GC or unimmunized for rubella.

congenital infections were reported among newborns from 2009 to 2011. No MTCT HBV infection was reported during the same period of time. Previous reports indicated that 30% of HIV or HBV-infected pregnant women can potentially transmit infections to their babies while up to 50% of syphilis–infected women can transmit infections to their children (Op de Coul *et al*., 2011). Based on the number of newborns infected relative to the number of newborns potentially at risk, the estimated percentages of prevented MTCT infection were 74.36%, 77.78% and 100% of HIV, syphilis, and HBV infections, respectively, were prevented (Table 3).

3.6 The effect of pregnant women age on the overall HIV, GC and CT prenatal screening tests.

Based on aggregate data, the association of age and the receipt of a prenatal screening test for all infectious diseases included in this study were assessed. These results indicated that out of the 79% of women who received a prenatal screen from 2006 to 2011, 97 to 100% of those screens requested testing for HBV, rubella and syphilis regardless of their ages and area of residence. Therefore, all subsequent discussion and analysis will focus only on HIV, CT and GC among screened women.

Estimated percentage of Congenital Infection (2009-2011)					
	Infected Pregnant Women	Transmission Risk	New Born at Risk	Infected New Born	% Prevention
HIV	13	30%	3.9	1	74.36%
Syphilis	9	50%	4.5	1	77.78%
HBV	102	30%	30.6	0	100%

Table 3: The estimated percentage of prevented MTCT infections among newborns from 2009 to 2011.

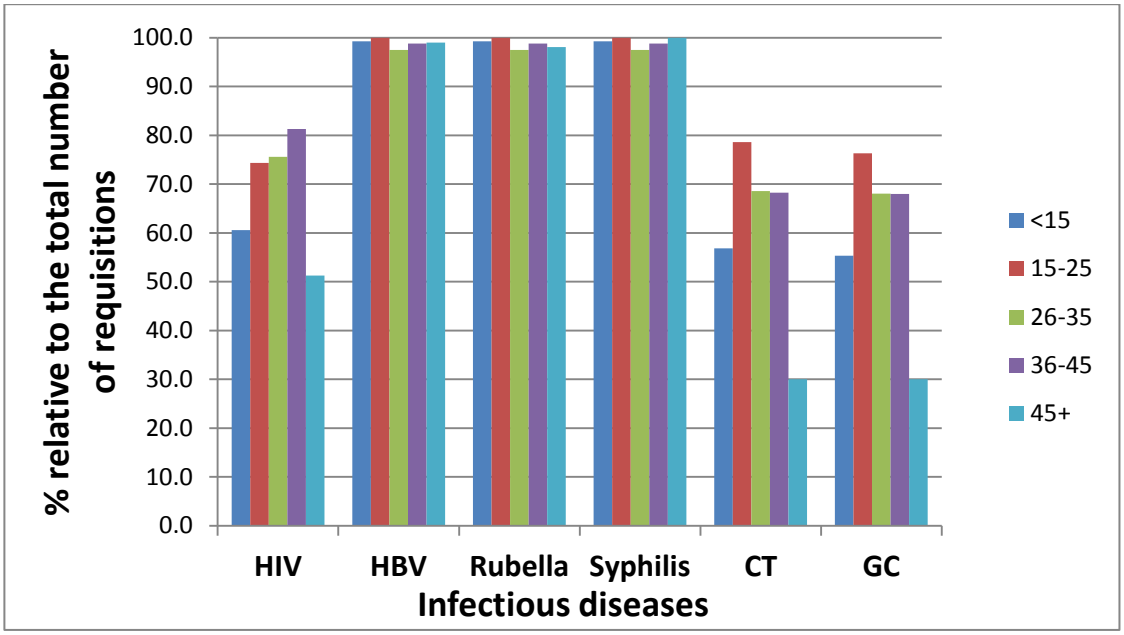
HIV testing was done significantly less frequently in the youngest <15 (60.6 ± 8.5%, p=0.007) and oldest > 45 (51.3 ± 5.7%, p=0.03) age groups in comparison with other age groups (16-25, 26-35, 36-45). Also, the oldest age group received significantly less CT (30 ± 5.2%, p=0.002) and GC (30 ± 5.2%, p=0.0017) screening tests than other age groups (Figure 5).

3.7 The effect of a pregnant woman age on the annual HIV, GC and CT prenatal screening tests.

By monitoring the annual adherence to HIV, GC, and CT among the 79% of screened pregnant women, results showed that requests for HIV prenatal screening tests increased annually in three age groups: 15 - 25 from 46.4 ± 1.5% in 2006 to 89.1 ± 0.9% in 2011 (p= < 0.0001), 26 - 35 from 55.9 ± 1.2% in 2006 to 82.9 ± 0.9 % (p = 0.0001), and 36 - 45 from 64.1± 2.7% in 2006 to 95 ± 1.2% (p < 0.0001). HIV prenatal screening tests in the youngest and oldest age groups tended to have an inverse U and U-shaped pattern, respectively, over time (Figure 6).

Similar to HIV testing, prenatal GC tests significantly increased in three age groups: 15 - 25 from 65.8 ± 1.4% in 2006 to 79.6 ±1.2% in 2011 (p= 0.0044), 26 - 35 from 55.8 ± 1.2% in 2006 to 65.3 ± 1.2% in 2011 (p=0.0356) and 36 - 45 from 52.3 ± 2.8 in 2006 to 76.3 ± 2.8% (p< 0.0001). A remarkable and remarkable noticeable drop in GC and CT testing (p< 0.0001) was observed in the youngest age group since 2008 (Figure 7 and 8).

A)



B)

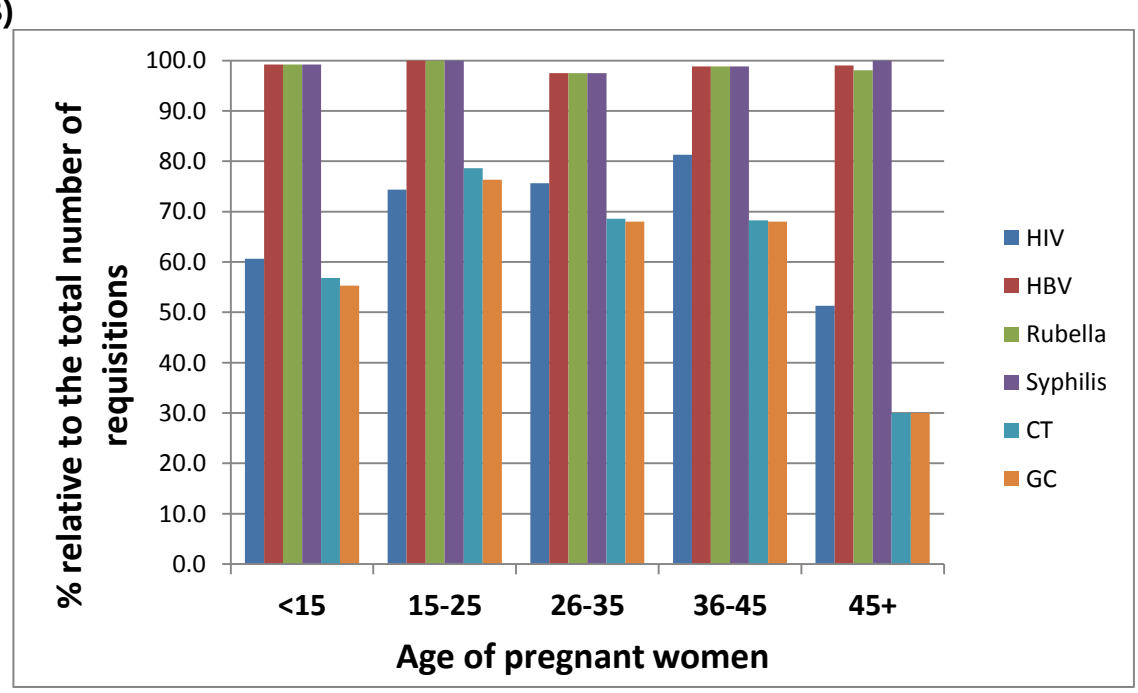


Figure 5: Relationship between age and prenatal screening. A) The effect of age on the adherence to prenatal screening of each infection **B)** The adherence to prenatal testing of infectious diseases in each age group. Results are represented as percentages relative to the total number of requisitions between 2006 and 2011.

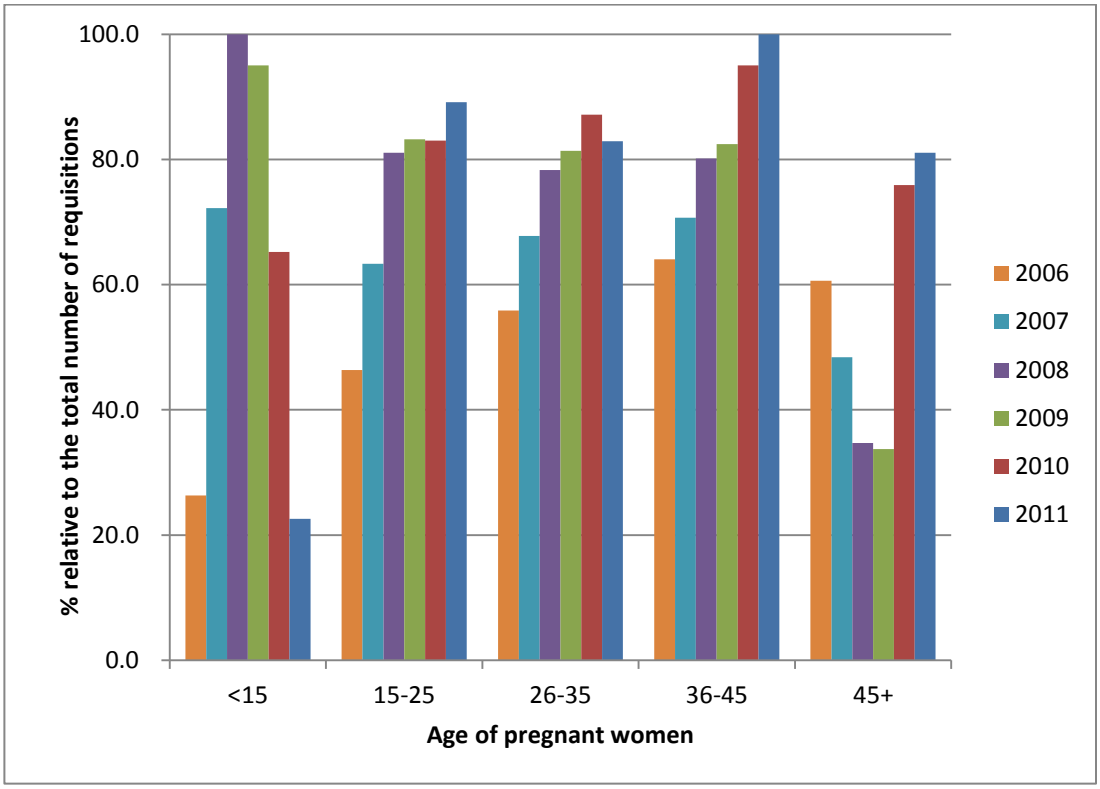


Figure 6: The change in adherence to HIV prenatal screening in each age group. Results are represented as percentages relative to the total number of requisitions reported each year.

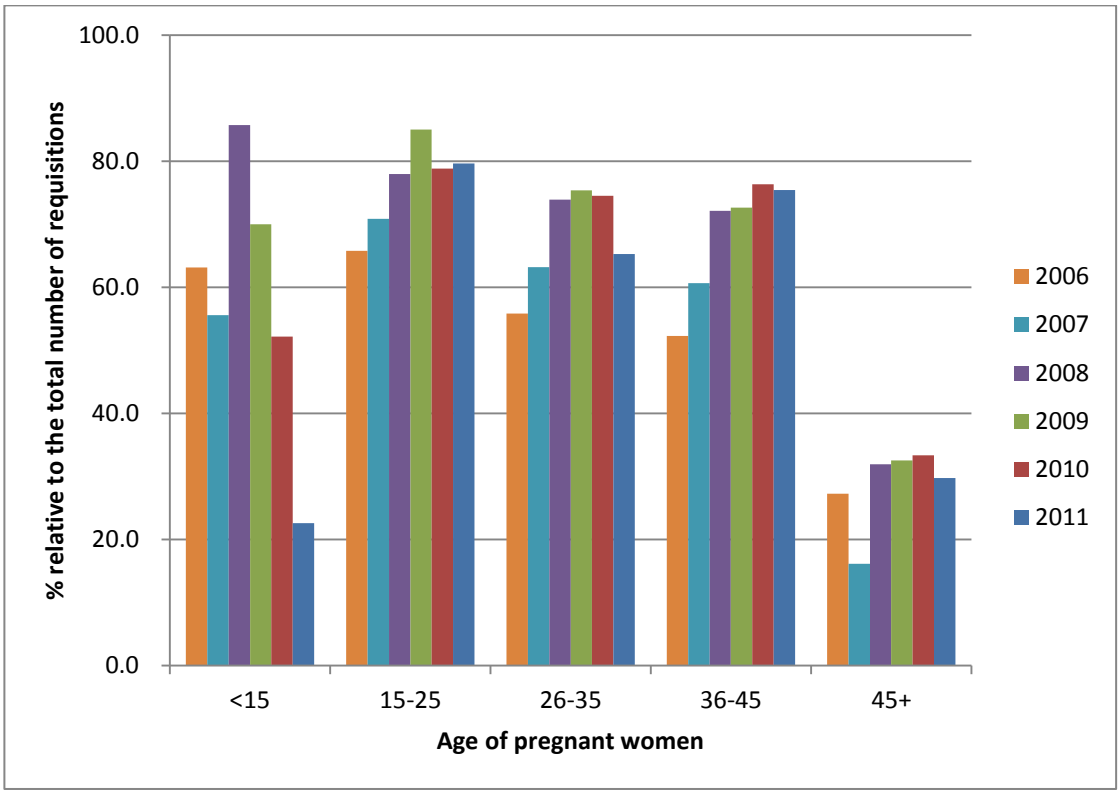


Figure 7: the change in adherence to GC prenatal screening in each age group. Results are represented as percentages relative to the total number of requisitions reported each year.

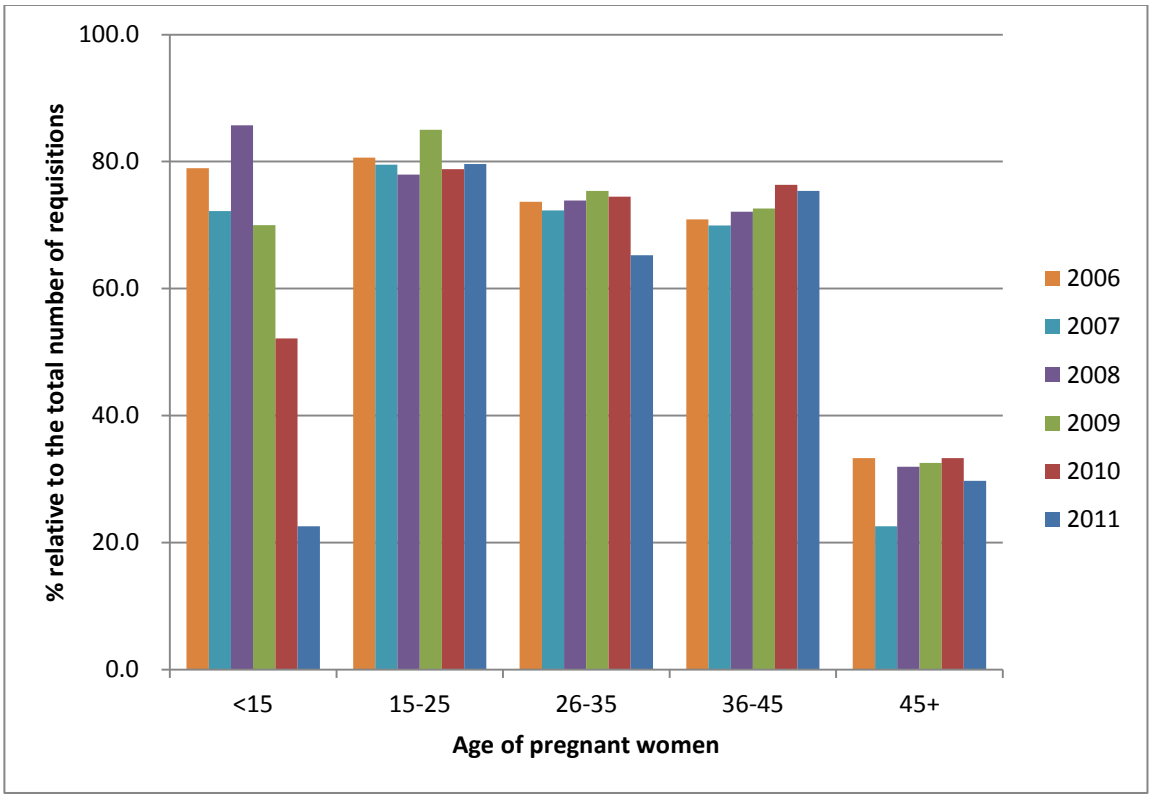


Figure 8: the change in adherence to CT prenatal screening in each age group. Results are represented as percentages relative to the total number of requisitions reported each year.

3.8 The effect of area of residence of pregnant women on the overall HIV, GC, and CT prenatal screening tests.

Based on the aggregated data available, the associations between area and the proportion of women who received the entire prenatal screening panel could not be assessed. Individual-level data would be required for this analysis. However, it was possible to assess testing patterns for the various infections across the different areas. Of the 79% of women who received some sort of prenatal screens, HIV prenatal testing was ordered significantly more frequently in 92.6 ± 0.3% of prenatal requisition forms of pregnant women living in Winnipeg ($p<0.0001$) in comparison with those in Brandon (63 ± 1.5%) and rural (62 ± 0.5%) areas. Also, residents of Winnipeg prenatal testing for CT (83.9 ± 0.4%) was not significant compared to Brandon (78.8 ± 1.3%) ($p= 0.362$) but significantly higher than rural areas (71.3 ± 0.5%) ($p= 0.028$). No significant differences by area were noted for receipt of a GC prenatal test (Figure 9).

3.9 The effect of area of residence of pregnant women on the annual HIV, GC, and CT prenatal screening tests.

HIV prenatal requests among screened women increased significantly in pregnant women who lived in Brandon from 0.2 ± 0.5% to 96.4 ± 1.4% ($p<0.0001$) and rural areas from 5.9 ± 0.6% to 90.2 ± 0.8 ($p<0.0001$). For residents of Winnipeg, rates of prenatal screening followed a U-shaped pattern with the lowest rates reported in 2008 ($p= 0.0001$) (Figure 10).

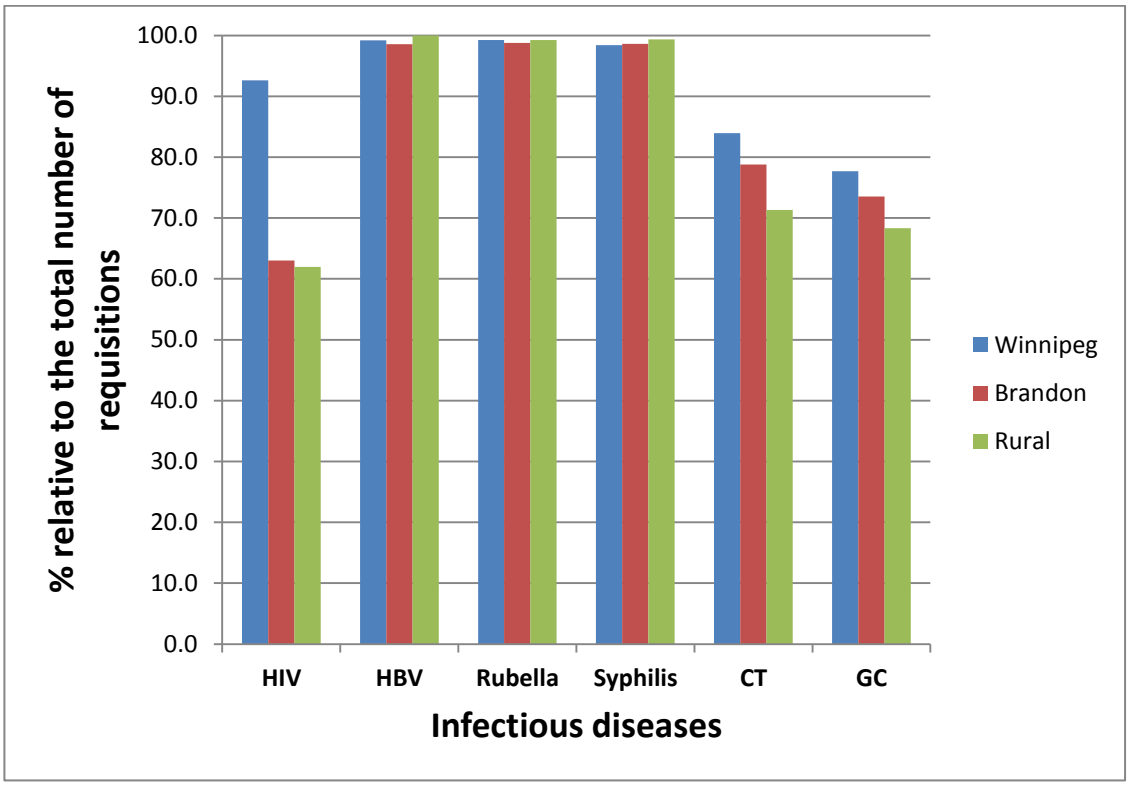


Figure 9: the effect of areas (urban versus rural) on prenatal screening. Results are represented as percentages relative to the total number of requisitions reported each year.

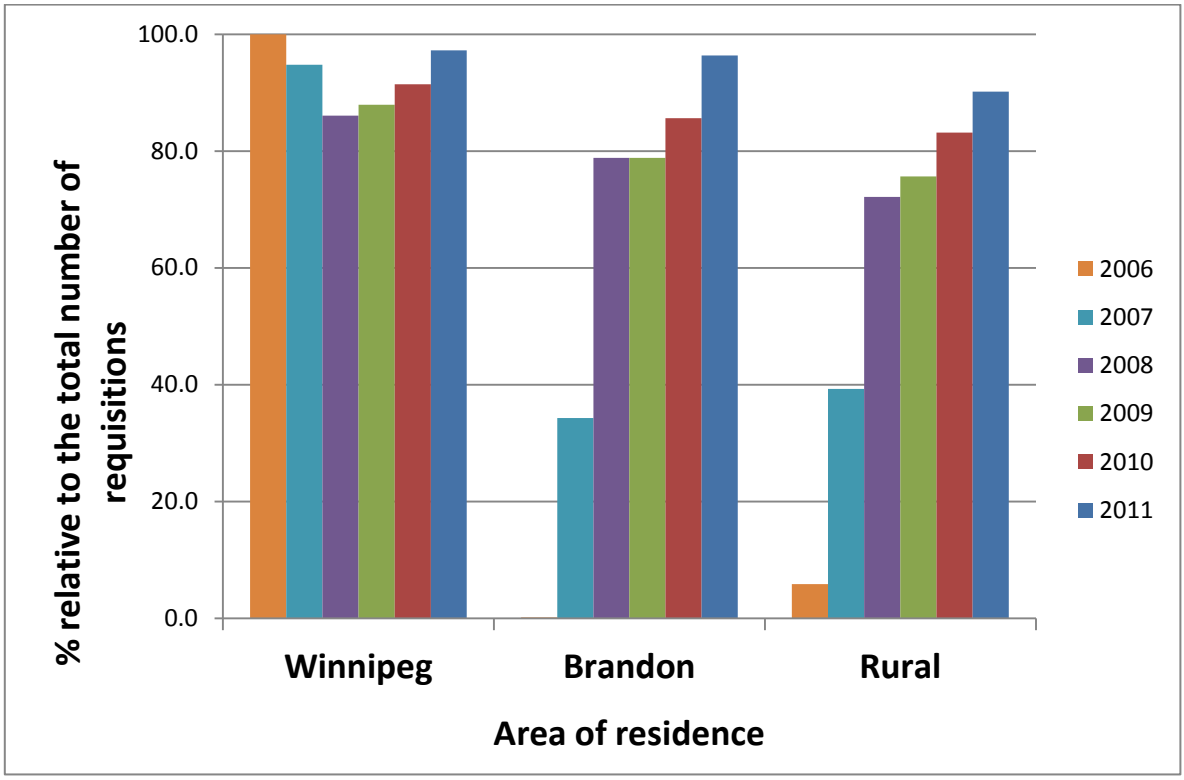


Figure 10: The effect of area of residence in HIV prenatal screening test. Results are represented as percentages relative to the total number of requisitions reported each year.

For GC prenatal testing, a relatively stable pattern was observed over all study years for residents of Brandon. Conversely, significant increases were noted in residents of Winnipeg from 60.8 ± 1.2 % in 2006 to 82.5 ± 1.2 % in 2011 (p= 0.0001) and rural areas from 56 ± 1.3 in 2006 to 75.5 ± 1.1 in 2011 (p= 0.0002) (Figure 11).

For CT, prenatal screening rates were between 60 to 80% of the total number of prenatal requisition forms from pregnant women living in the three areas. However, a remarkable spike in CT prenatal testing (100 ± 0.4 %, p= 0.0026) was observed in residents of Brandon in 2007 (Figure 12).

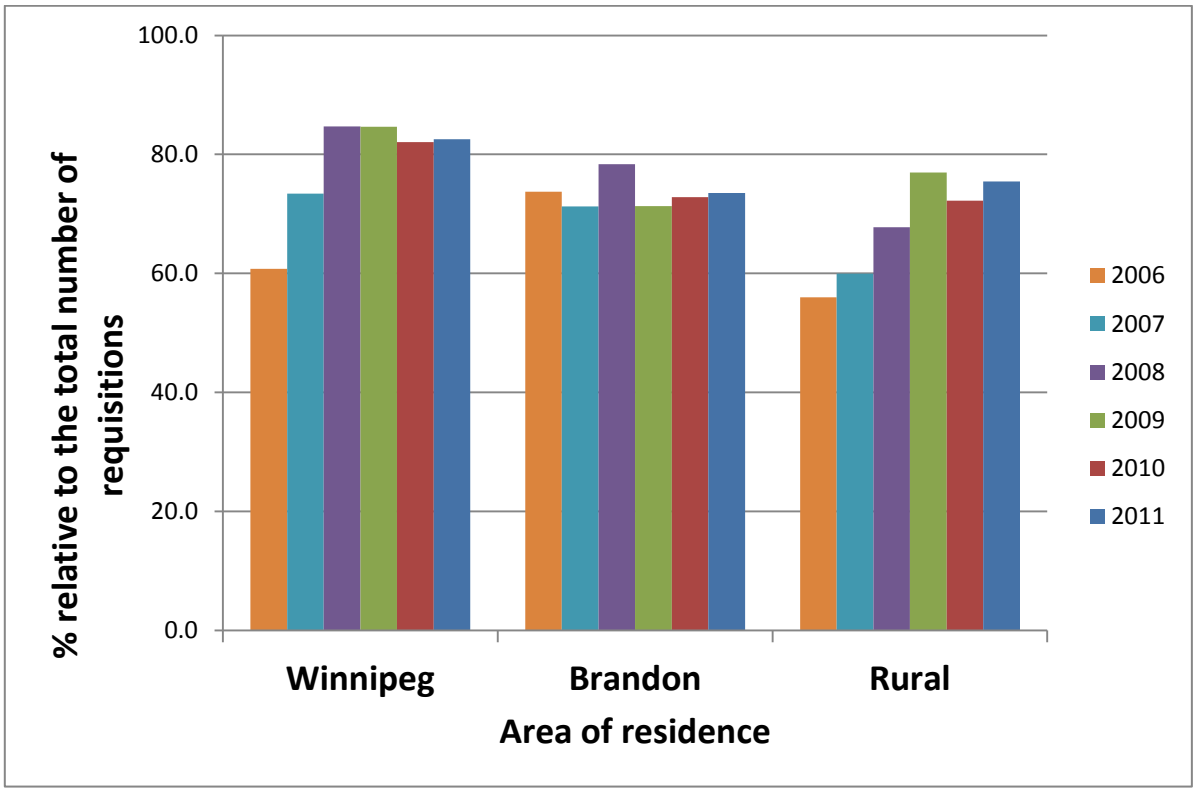


Figure 11: The effect of area of residence in GC prenatal screening test. Results are represented as percentages relative to the total number of requisitions reported each year.

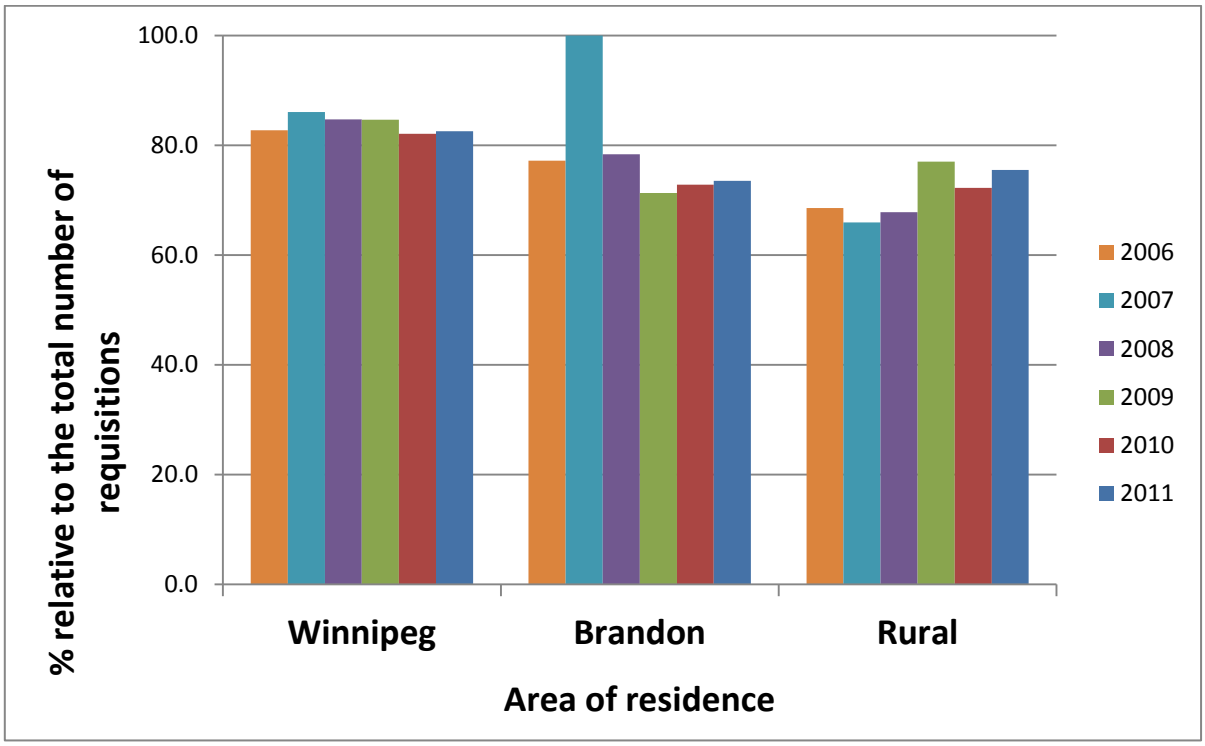


Figure 12: Association between area of residence and CT prenatal screening test requests. Results are represented as percentages relative to the total number of requisitions reported each year.

4. Discussion

Prenatal screening for infectious diseases plays a critical role in identifying pregnant women at risk of vertically transmitting infections to their infants at any stage of pregnancy (Schrag *et al*; 2003). Early detection of women with infections allows timely initiation of suitable medical interventions and provision of appropriate advice when needed (Schrag *et al*; 2003). Different preventative strategies exist for each infection. For instance, prenatal HBV can be prevented using immunoglobulin and a vaccination program for exposed infants (Mast *et al*; 2007), CRS can be prevented by administration of MMR vaccination for women at reproductive ages to protect future pregnancies. Prenatal HIV infection is preventable by administration of ART to both pregnant women and their newborns in addition to consideration of caesarean section for infected mothers when required (Connor *et al*; 1994).

In Manitoba, sexually transmitted and blood borne infections (STBBIs) prenatal screening is recommended for all pregnant women (Centers for Disease Control and Prevention., 2010). It is important to mention that during the study period two versions of requisition forms were used in CPL: pre and post 2008. Modifications were done on the old form to make it easier and more effective for ordering practitioners. These modifications include adding boxes adjacent to possible tests instead of writing down each test requested. In addition, a specific check box for a prenatal panel was added for the common STBBIs. CT and GC tests were performed simultaneously on a single sample resulting in identical CT and GC screening rates since 2008.

The initial goal of the present study was to assess the rate of pregnant women in Manitoba screened for potential STBBIs and evaluate the overall adherence to prenatal screening program recommendations. In addition, the effectiveness of screening for STBBIs and preventing subsequent MTCT infections was determined. Furthermore, the relationship between prenatal screening and patient demographics (e.g., ages and areas of residence) was determined to aid in finding potential barriers or trends in suboptimal prenatal STBBIs screening rates.

This study was performed to ensure information was current, and help target any gaps in prenatal program coverage between 2006 and 2011 in Manitoba. The overall rates of prenatal screening of STBBIs as per recommendations in Manitoba were sub-optimal. Only 79.3% of pregnant women received prenatal screening for at least one of the potential infectious diseases included in this study. This means that approximately one fifth of pregnant women missed the opportunity to be screened for any of the infectious diseases where interventions were possible and of clear benefit. Moreover, prenatal STBBI testing rates over the six years of assessment declined considerably from 83.7% in 2006 to 69.6% in 2011. These results could suggest insufficient awareness about the importance of prenatal screening among the public and health care providers. Thus, further analyses were conducted in order to identify major factors that could be associated with decreased prenatal testing rates.

As there is a possibility that some pregnant women were screened for some infections but not for others, the rate of pregnant women who received prenatal screening tests was determined and categorized according to the types of infection. Documented HIV, CT and GC screening among pregnant women was less common in comparison with HBV, rubella and syphilis in the overall population. Interestingly, the screening rates for HBV, rubella, and syphilis were similar even before the introduction of the new requisition form. Although HIV test is also part of the prenatal panel, the number of screened women for HIV is lower than the other infections in the same panel probably due to the opt-out option. Pregnant women may refuse HIV screening after discussing the significance of prenatal testing for HIV and the availability of medical interventions that can efficiently prevent. According to a study that was conducted in Malawi, many women who have been tested in previous pregnancies defer testing in the subsequent ones (Van Lettow *et al*; 2012). Other groups refused to be tested because they were concerned about testing confidentiality (Van Lettow *et al*; 2012). In addition, Kalichman and Simbayi have studied patient's attitudes regarding HIV testing and they found that the fear of stigma and discrimination have a high impact on refusing HIV screening acceptance (Kalichman and Simbayi; 2003). All of these explanations can be reasons for the low number of pregnant women tested for HIV in Manitoba. CT and GC testing have been performed together since 2008. The small difference in the rate of screened women between CT and GC could reflect the period

before 2008 when each test was requested separately and, thus, the ordering practitioners might have requested one test but not the other.

To give better insight about the testing rate of each infection over the study period, the change in the testing rates for each infection was evaluated. A significant decline in the rate of prenatal screening tests for each of HBV, rubella and syphilis was recognized. The rate of CT and GC testing was relatively stable over time with a slight decrease in 2011. Interestingly, only the rate of HIV testing shows a remarkably steady increase over years attaining 65.9% in 2011. This increase can be due to the increases in practitioner's awareness in the last few years about the importance of ordering HIV test in preventing MTCT infection (Remis *et al*; 2012). In Manitoba, there has been considerable education and advocacy for HIV by a provincial HIV Clinical Program. In addition, different studies have shown that the implementation of an opt-out strategy in HIV testing can increase the rate of HIV prenatal screening uptake (Walmsley; 2003, Deblonde *et al*; 2007, and Giraudon *et al*; 2009).

Medical practitioners, patients, and other factors might have contributed to the low prenatal screening rate. Conaty *et al* have reported that some practitioners depend on previous tests results from earlier pregnancies and do not request new testing for the current pregnancy (Conaty *et al.,* 2005). Also, some pregnant women may not present for screening through the whole period of pregnancy and only present to medical attention at delivery. Other studies identified several economic, social, marital statuses, level of education, and religious factors that affect prenatal screening rates in different countries. For

instance, Schrag and colleagues suggested that black women are less likely to undergo prenatal screening than whites due to color discrimination in the US (Schrag *et al*; 2003). In Brazil, low income and level of education in single women are markers for women not tested for HIV and syphilis (Rodrigues *et al*; 2008). A study conducted by Sheikh and colleagues to assess the adherence to screening program recommendations and determine factors contributing to prenatal screening found that lack of insurance has a negative impact on testing rates (Sheikh *et al*; 2009).

Herein, the differences in the prenatal screening practice for each infection were evaluated and categorized according to the age of the pregnant women and the area of residence within the province. Results indicated that there is a strong relationship between the age of pregnant women and prenatal screening testing rates. The rate of screened pregnant women received prenatal screening tests for HBV, rubella and syphilis ranges between 97.5% and 100% across all age groups. Data indicated that the rate pregnant women received prenatal screening tests for HIV was considerably lower in the youngest (under 15 year old) and the oldest (older than 45 year old) age groups versus other age groups. An upward trend in the rate of pregnant women screened for HIV infection was noticed in the age groups 15 - 25, 26 - 35 and 36 - 45.

The rate of pregnant women screened for CT and GC was significantly lower in the oldest age group versus other age groups. A study released in 2002 suggested that the low rate of screened pregnant women of older age groups might be due to the availability of previous negative tests results from

their earlier pregnancies (Hogben; 2002). Therefore, their health care providers were less concern about retesting in the current pregnancy (Hogben; 2002).

By following the trend of women screened for CT and GC over the six years of this study, no difference was recognized in the rate of pregnant women receiving CT and GC prenatal screening across all age groups, except the youngest age group, which shows a significant decrease from year to year. Similar to our findings, Schrag and colleagues have reported that pregnant women less than 20 years old are more likely to receive inadequate prenatal care than other age groups (Schrag *et al*; 2003). Lower levels of education and less awareness about the importance of prenatal care in women less than 15 years old might be the reason for this group's inadequate STBBI prenatal screening.

In addition to age of pregnant women, the study demonstrates that the rate of pregnant women who received prenatal screening is different across areas (Winnipeg, Brandon, and rural areas). The rate of pregnant women receiving prenatal screening for HBV, rubella, and syphilis was significantly higher in all areas in comparison with HIV, CT and GC. HIV, CT and GC screening rates were considerably higher in Winnipeg whereas rural areas had the lowest prenatal screening rates for these infections.

The number of pregnant women screened for HIV infection during their pregnancy increased significantly from year to year in both Brandon and rural areas. In Winnipeg, the rate of pregnant women screened for HIV follow a U-shape pattern during the six year of the analysis. In all areas, the rate of

pregnant women received prenatal screening for CT and GC remained levelled since 2008. This is likely attributable to a testing policy change rather than a practitioner practice change.

These results will be helpful in directing medical resources and education to areas at highest risk for STBBI MTCT as dictated by lower screening rates. The rate of unscreened pregnant women for HIV, CT and GC are considerably lower in rural areas. A study conducted in rural India show that some pregnant women with low income cannot afford transportation or time off work to visit health care facilities (WHO., 2009 and Helleringer *et al.,* 2009). This may also applied in pregnant women living in rural Manitoba. Practitioners providing prenatal care may also be limited in rural settings. It also may be explained by limited knowledge on prenatal screening significance and prevention measures availability. Lack or low level of health care facilities in these areas may have an impact on low rate of screened women. Therefore, rural areas should provide an ideal target to direct education regarding the importance of prenatal STBBI screening and PMTCT and resources to facilitate testing in these locations. Ideally, healthcare for women in pregnancy should not be affected by area of residence.

The importance of prenatal screening program in identifying pregnant women with infections and preventing MTCT of infectious diseases was also addressed in this study. Approximately 0.3%, 1% and 6% of screened women were reported positive to HBV, GC, and CT infections, respectively. HIV and syphilis cases were also identified. The rate of these two infections was higher

in screened women versus general population probably because pregnant women are more likely to receive screening for STIs than general population. Also, pregnant women are a subgroup of the population who have demonstrated that they have had sexual intercourse. A proportion of the general population has not which would likely account for lower rates. (PHAC., 2008 and Manitoba Health., 2011). Although the rate of positive cases is low among pregnant women screened for infectious diseases, the need for prenatal screening is essential to detect pregnant women with infections and avert transmission to infants.

Analysis also showed that 90% of screened women have IgG for rubella infection and, thereby, resistant to the infection. It is likely due to early immunization against rubella during childhood. This should raise a question about the effectiveness of providing rubella prenatal screen for those previously immunized against the infection.

Introduction of prenatal screening programs have significantly reduced the number of MTCT infections between 2009 and 2011. According to this study, out of 13 HIV infected pregnant women detected through prenatal screening, 12 infants at risk have been prevented from acquiring the infection from their mothers. The one case of HIV MTCT occurred in a woman who was aware of her status but failed to get antiretroviral therapy. Syphilis infection was prevented in 8 out of 9 infants born to infected mothers. Interestingly, none of the infants born to HBV infected mothers (102 cases) acquired the infection. The availability of HBV vaccination and immunoglobulin is likely the reason for

the 100% prevention rate among newborns. Both adequate and timely treatments such as antivirals, antibacterial, and vaccinations are required in order to efficiently prevent MTCT. Prenatal screening program plays a critical role in early identification of infected women, and allows timely medical interventions when required.

The present findings suggests a need for overall improvement and enhancement of the current practice to reach acceptable, satisfactory and sufficient adherence to prenatal screening regulations and guidelines for these infection in our province.

4.1 Translation Significance

Prenatal screening programs and the appropriate interventions recommendations was found to be very effective in preventing MTCT infection and, consequently, in preventing or minimizing significant morbidity and initial mortality. The present study highlights the need for education and resources to improve adherence to prenatal screening program regulations. In particular, it is crucial to increase the awareness of young women (less than 15 years old) about STBBIs and the significance of early prenatal screening and appropriate medical interventions. It is also worthwhile to invest in educating cultural groups in Manitoba who refuse to consider some prenatal tests (e.g., HIV screening) for cultural and religious reasons. Health care providers in hospitals, clinics and medical centers should be aware of the need to consider prenatal screening for all infections in every pregnancy and, not to rely on results from earlier

pregnancies. Conducting further assessments on why residents of rural areas are less likely to receive prenatal screening is of a great importance in order to diagnose and solve the problem. Continuous or periodic evaluation of adherence to prenatal screening of infectious diseases recommendations in Manitoba is extremely important in providing up-to date knowledge regarding the current practice in the province.

4.2 Study Limitations

The first limitation of this study is that all patients' information was entered manually into CPL databases. Therefore, there is always a chance of human error in the available information. In addition, the underlying reason, in terms of why a given woman has not been screened for specific pathogens and why a particular test was not regularly carried out, were impossible to determine as only associations can be drawn.

The rate of prenatal HIV screening uptake is likely to be slightly higher than what result showed due to the inability to include pregnant women who chose non-nominal testing though this is likely of small impact. Since this study was based in Manitoba, results cannot be generalized to other provinces in the country. In general, the fact of underestimation screening uptake is always possible with women who lost their babies before receiving prenatal testing. Also, data extraction was based on distinct PHINs in which each distinct PHIN was counted only once in a given year. The chance of the same women to get pregnant twice in the same year is very rare but still possible, and this might have

resulted in underestimation of screening uptake analysis. In addition, a woman who was found to be either HIV or Hep B Ag positive prior to her pregnancy would not need to be tested in pregnancy as they have already been identified. Therefore, the number of HIV and Hep B positive pregnant women who delivered during the period of our study is under-estimated.

Some patients information such as patient`s age, area of residence, or test result were missing in a number of prenatal requisitions received in this study. This had little impact on some analysis. For instances, the rate of infection positivity among pregnant women was determined between 2009 and 2011 rather than the whole period of the study.

Information on the number of pregnant women infected with HBV and syphilis and the number of MTCT of HBV and syphilis infection between 2006 and 2008 was unavailable. Also, the number of pregnant women infected with HIV in 2008 was missing. Moreover, some prenatal requisitions were excluded from demographic factors analysis.

5. Conclusion remarks:

Infectious diseases during pregnancy can harm both women and infants if not treated. Prenatal screening of pregnant women allows early diagnosis of infection, and helps to limit transmission to infant by utilizing appropriate preventative and therapeutic interventions. The results of this study indicate that prenatal testing for potential infectious diseases in Manitoba is suboptimal and distinct patterns are evident which may allow for targeted resource allocation to

improve STBBI screening rates. The presence of women not screened for one or more STBBIs is clearly contradictory to the Manitoban guidelines for preventing MTCT infections. Therefore, it is important to reinforce prenatal screening uptake and strengthen the capacity of diagnosing infectious diseases in all health care facilities within Manitoba. In addition, more efforts are essential to increase the rate of prenatal testing and adherence to screening guidelines in our youngest age group (less than 15 years), women above 45 years old and those who live in rural areas. Following targeted education and resource allocation, future work must include monitoring prenatal screening rates in the province to determine effectiveness and adherence to current provincial recommendations.

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7. Appendix

A)

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Boards

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR: Mr. A. Fazio	**INSTITUTION/DEPARTMENT:** UofM / Medical Microbiology	**ETHICS #:** HS15720 (H2012:310)
APPROVAL DATE: November 7, 2012	**EXPIRY DATE:** November 7, 2013	
STUDENT PRINICIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. J. Bullard		

PROTOCOL NUMBER: NA	**PROJECT OR PROTOCOL TITLE;** Screening tests for congenital infectious diseases in Manitoba: are all pregnant women in Manitoba screened for potential congenital infections? *formerly Screening tests for congenital infectious diseases in Manitoba: are all pregnant women in Manitoba screened for potential congenital disease?*
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: NA	

Submission Date of Investigator Documents: November 2, 2012	**HREB Receipt Date of Documents:** November 2, 2012

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol: Proposal received September 6, 2012		
Consent and Assent Form(s):		
Other: Data Capture Sheet		01/08/12

CERTIFICATION
The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255/ **Fax:** (204) 789-3414

B)

Manitoba

Health
Health Information Privacy Committee
4043 – 300 Carlton Street
Winnipeg, MB R3B 3M9
T 204-786-7204 F 204-944-1911
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January 25, 2013

Ms. Arwa Faizo
University of Manitoba
1608 – 160 Smith Street
Winnipeg, MB R3C 0K8

File No. 2012/2013 - 45

Dear Ms. Faizo:

Re: Screening Tests for Congenital Infectious Diseases in Manitoba: Are all pregnant women in Manitoba screened for potential congenital infections?

The Health Information Privacy Committee has considered and ***approved*** your request for access to data for the purposes of the above named project.

Any significant changes to the proposed study design should be reported to the Chair/HIPC for consideration in advance of their implementation. Also, please be reminded that *all manuscripts and presentation materials resulting from this study must be submitted for review at least 30 days prior to being submitted for publication or presentation.*

Please note that a Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by MH. If you have any questions or concerns, please do not hesitate to contact Lisa LaBine, Committee Coordinator at 204-786-7204.

Yours truly,

[redacted]

D. Biehl, MD, FRCP
Chair, Health Information Privacy Committee

Please quote the file number on all correspondence

c.c. D. Malazdrewicz
J. Bullard

Manitoba
spirited energy