

# Prevalence and Genetic Diversity of Hepatitis B and C Viruses Among Couples Attending Antenatal Care in a Rural Community in Rwanda

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## ABSTRACT

**Background:** Globally, over 325 and 170 million people are infected with hepatitis B virus (HBV) and hepatitis C virus (HCV), respectively. If untreated, these infections can progress to cirrhosis or hepatocellular carcinoma. The primary aim of this study was to determine the prevalence, genetic diversity, and factors associated with HBV and HCV among couples attending antenatal care in rural Rwanda.

**Methods:** This was a cross-sectional survey of HBV and HCV seroprevalence. Study participants were administered a brief structured questionnaire to obtain information on sociodemographic and behavioural risk factors for HBV and HCV. Participant blood samples were screened for hepatitis B surface antigen (HBsAg) and anti-HCV antibodies (anti-HCV) using rapid diagnostic kits; confirmatory testing was done by enzyme immunoassay and nucleic acid tests. HBV genotypes were determined using nested polymerase chain reaction; HCV genotypes were determined by reverse transcriptase PCR followed by hybridisation with sequence-specific oligonucleotides. Statistical associations between risk factors and infection status were determined using Chi-square tests and bivariate logistic regression.

**Results:** In total, 220 individuals participated in the study. This includes 110 pregnant women and 110 male partners who were attending antenatal care at Gitare and Cyanika health centres. Two participants (0.9%) had serological evidence of HBV infection, and 4 participants (1.8%) were infected with HCV. HBV genotype A accounted for all HBV infections; HCV genotype 4 accounted for all HCV infections. None of the assessed factors were associated with HBV infection while occupation type and scarification were significantly associated with HCV infection (*P* values were .03 and <.01 respectively). All cases of infection were discordant with their respective partners.

**Conclusion:** Prevalence rates of HBsAg and anti-HCV are low in couples attending antenatal clinics in rural Rwanda. Consideration should be given to interventions aimed at reducing the risk of transmission in discordant couples and infants of infected mothers.

## INTRODUCTION

Globally, hepatitis B and C viral infections account for a considerable proportion of morbidity and mortality from liver disease. In 2015, an estimated 257 million individuals worldwide had chronic hepatitis B virus (HBV) infection, leading to approximately 887,000 deaths.<sup>1</sup> During the same period around 71 million people were chronically infected with hepatitis C virus (HCV); each year approximately 1.7 million people are newly infected with HCV and 400,000 HCV-related deaths occur.<sup>1</sup>

Prevalence rates of HBV and HCV vary widely between world regions and countries.<sup>2</sup> Hepatitis B surface

antigen (HBsAg), a marker of active infection, has a prevalence rate >8% in several African countries, including Nigeria, Namibia, Gabon, Cameroon and Burkina Faso. HBsAg prevalence is intermediate (2%-8%) in Kenya, Zambia, Ivory Coast, Liberia, Sierra Leone, Senegal and Rwanda, and low (<2%) in North Africa.<sup>3,4</sup> Survey data indicate that HBsAg prevalence in Rwanda is 1.9% to 3.2% among blood donors and 3.7% among pregnant women attending antenatal clinics.<sup>5</sup> Based on studies of small patient groups and data from neighbouring countries, in Rwanda, the prevalence of anti-HCV antibodies (anti-HCV) is estimated to be 3.1% in the general population and 4.7% among people living with HIV.<sup>6-8</sup>

Globally, in 2015, there was an estimated 1.75 million new HCV infections. The availability of effective antiviral treatment has revolutionised treatment prospects, although access to treatment remains a significant challenge for most developed countries and remains out of reach for developing nations. However, the incorporation of hepatitis B immunisation into the expanded immunisation programmes has led to substantial decreases in chronic hepatitis B infection rates in children.<sup>9,10</sup>

In addition to variations in prevalence, HBV and HCV display genotypic diversity between world regions and countries. HBV has 10 well-described genotypes (A to H), and 2 genotypes that are tentatively defined according to their genome divergences (I and J).<sup>11-13</sup> People infected with HBV genotypes A or C are at a higher risk of progressing to chronic hepatitis than those exposed to genotypes D and B; nevertheless, all genotypes can lead to acute or chronic infections.<sup>14</sup> In Africa, genotype A predominates in Southern and Eastern Africa, genotype D predominates in northern Africa, and genotype E predominates in the vast region from Senegal to Namibia and eastward to the Central African Republic.<sup>3</sup> In Rwanda, HBV genotypes A, B, C, D and E have been reported.<sup>6,15</sup> HCV has 6 well-described genotypes (1 to 6)<sup>16,17</sup> and 5 genotypes that are tentatively defined (7 to 11).<sup>11-13</sup> Genotype 1 accounts for about 46% of all HCV infections, genotype 3 accounts for about 30% of HCV infections, and genotypes 2, 4, 5, 6 collectively account for about 24% of HCV infections.<sup>18</sup> Recent studies have correlated the different HCV genotypes with varying levels of risk of disease progression and varying responses to antiviral therapy.<sup>19,20</sup> In Rwanda, HCV genotypes 1 and 4 predominate.<sup>6,15,21</sup>

To reduce the burden of HBV-associated liver disease, in 2002 Rwanda introduced universal administration of the HBV vaccine in neonates; thus, most youth born from 2002 onwards are protected from HBV infection. However, perinatal transmission, which accounts for the majority of HBV transmission worldwide, continues to occur in Rwanda.<sup>22,23</sup> In adults, sexual transmission and risky behaviour, including injection drug use, tattooing, body piercing, and scarification without using sterilised equipment are also routes of HBV transmission.<sup>24,25</sup> Routes of ongoing HCV transmission in Rwanda remain unknown, but prevalent cases are thought to have resulted from unsafe injection and blood transfusion practices in earlier eras.<sup>21</sup>

In 2012, Rwanda initiated a viral hepatitis B and C control programme. The programme was intensified in 2015 with the introduction of more efficacious treatments for HCV. For Rwandans chronically infected with HBV, tenofovir and entecavir are available at all public health facilities offering HIV services.<sup>26</sup> These drugs have been shown to suppress HBV viral replication and prevent disease progression and subsequent mortality. For treatment of HCV infection, ribavirin, ledipasvir, daclatasvir and Harvoni (ledipasvir + sofosbuvir) are being used.<sup>26</sup> The programme includes primary prevention activities to reduce infection by increasing awareness of HBV

and HCV in the general and high-risk populations. Secondary and tertiary prevention activities focus on early detection of HBV and HCV, timely treatment to prevent progression to liver disease, and targeted HBV vaccination of high-risk populations.<sup>26</sup>

National guidelines recommend screening and treatment of hepatitis infections in pregnant women and their partners.<sup>26</sup> There are 2 separate rapid diagnostic tests routinely implemented: 1 designed to detect HBsAg for HBV screening and another to detect anti-HCV antibody for HCV screening. However limited implementation of these guidelines has undermined the efficiency of universal neonatal HBV immunisation, which is normally given at 6 weeks of age, but is given within 24 hours of birth in combination with hepatitis B immunoglobulin when the mother is recognised to be HBV positive.<sup>25,27</sup>

We conducted the current study to provide data on prevalence rates, genotypes and risk factors for HBV and HCV infection in couples attending antenatal clinics in rural Rwanda. These data may inform the country's viral hepatitis disease control programme, aimed at reducing perinatal and sexual transmission.

## METHODS

### Study Design and Setting

We conducted a cross-sectional study from August 2017 to February 2018 to assess the prevalence and genetic diversity of HBV and HCV among couples attending antenatal clinics in rural Rwanda. The study was carried out at 2 randomly chosen health centres, Gitare and Cyanika, located in Burera District, Northern Rwanda; these health centres serve a population of 57,805 people<sup>28</sup> and are adjacent to borders of Ugandan and Democratic Republic of Congo border.

### Sample Size

We determined the minimum sample size using Fisher's formula for cross-sectional studies,<sup>29</sup> assuming an HBsAg prevalence rate of 5%<sup>6</sup> and an anti-HCV prevalence rate of 4%.<sup>27</sup> The minimum sample size was estimated by Fisher's formula expressed as samples size (SS) =  $[Z^2 P(100-P)] / \epsilon^2$ , where, Z is the value (1.96 for 95% confidence level [CI]), P represents, and  $\epsilon$  is the minimal tolerable error at 95% CI, expressed as a decimal (0.05). This formula yielded a minimum sample size of 73. To increase precision, an anticipated design effect of 3 was applied to yield a final sample of 220.

### Data Collection and Diagnostic Procedures

Participants were recruited as couples during routine antenatal clinic visits. Participants were consecutively recruited from antenatal clinics; only those who met the enrolment criteria were invited to participate in the study.

Couples were recruited at health centres. Inviting men to accompany women to antenatal clinic is considered an important strategy for reducing maternal morbidity and mor-

**TABLE 1.** Distribution of Hepatitis B Surface Antigen and Anti-HCV Seroprevalence Rates Across Sociodemographic Characteristics

Variables		HBsAg Detected n (%)	P Value	Anti-HCV Detected n (%)	P Value
Age, years					
18-30	129	1 (0.8)	.88	1 (0.8)	.84
31-40	72	1 (1.4)		3 (4.2)	
41-50	16	0 (0.0)		0 (0.0)	
>51	3	0 (0.0)		0 (0.0)	
Gender					
Male	110	1 (0.9)	.75	2 (1.8)	.68
Female	110	1 (0.9)		2 (1.8)	
Education level					
None	48	1 (2.0)	.74	1 (2.0)	.07
Primary	120	1 (0.8)		1 (0.8)	
Secondary	41	0 (0.0)		0 (0.0)	
Tertiary	11	0 (0.0)		2 (18.2)	
Occupation					
Not employed	132	2 (1.5)	.71	1 (0.8)	.04
Private sector	13	0 (0.0)		1 (7.7)	
Public sector	8	0 (0.0)		1 (12.5)	
Self-employed	67	0 (0.0)		1 (1.5)	

tality by enabling couples to sufficiently prepare for birth and avoid care-seeking delays for obstetric emergencies. Presently, Rwanda records a distinctly high number of attending partners – 87% at the first visit – resulting from previous campaigns done by community health workers.<sup>30</sup> We excluded couples who had a prior history of HBV vaccination as well as couples in which at least 1 partner was undergoing treatment for HBV or HCV infection.

After obtaining written informed consent, study participants were administered a structured one-on-one interview to obtain information on sociodemographic factors, medical history and risk factors for HBV and HCV. A 5 ml venous blood sample was collected for HBV and HCV screening by rapid diagnostic test (RDT), confirmatory testing and genotype

analysis. RDT results were communicated back to the study participants within 45 minutes of blood collection; confirmed results were communicated to participants. Participants with a confirmed positive test result for HBV or HCV were counselled and referred to hospital for clinical management. The unused portions of the samples were transported to Kigali to retest the same samples using advanced diagnostic tests (enzyme-linked immunosorbent assay for HBV and polymerase chain reaction [PCR] for HCV), as recommended by national guidelines. All positives samples were also positive upon re-testing, and we invited those who were confirmed positive to provide another 5 ml of blood for genotype testing (as the manufacturers' instructions recommended whole fresh blood samples). The genotypes results were available after

**TABLE 2.** Distribution of HCV Infection Across Behavioural and Medical History Factors

Variables	Participants n	Anti-HCV Detected n (%)	P Value
Knowledge of HCV infection			
Yes	30	1 (3.3)	.50
No	190	3 (1.5)	
Intravenous user			
Yes	11	0 (0.0)	
No	209	4 (1.9)	
Multiple sex partners			
Yes	40	2 (5.0)	.09
No	180	2 (1.1)	
History of scarification			
Yes	21	2 (9.5)	<.01
No	199	2 (1.0)	
History of body piercing			
Yes	2	0 (0.0)	.84
No	216	4 (1.9)	
History of tattooing			
Yes	3	0 (0.0)	.81
No	217	4 (1.8)	
Ever had blood transfusion			
Yes	11	0 (0.0)	.64
No	209	4 (1.9)	
Ever had hospital admission			
Yes	80	1 (1.3)	.68
No	140	3 (2.1)	

*Continued*

one month and were communicated to the respective participants.

RDT screening for HBsAg was done using Cypress Diagnosis anti-HBsAg Dipstick, Langdorp, Belgium;<sup>31</sup> RDT screening for hepatitis C virus IgG (anti-HCV) was done using SD BIOLINE HCV One Step Hepatitis C Virus Test (Standard Diagnostics Inc., Korea).<sup>32</sup> RDT results were confirmed by enzyme immunoassay (EIA) using the Murex HBsAg kit (version 3; Murex Biotech, Dartford, Kent, United Kingdom).<sup>33</sup> Confirmed HBV-positive samples were genotyped using hybridisation with sequence-specific oligonucleotides. The PCR products were electrophoresed on 2% agarose gels stained with ethidium bromide and examined under UV light using the Bio-Rad Gel Doc 2000 System (Bio-Rad Laboratories, Segrate, Milan, Italy).<sup>34</sup> For HCV positive samples, viral load and genotype were determined by the reverse transcriptase-PCR (RT-PCR) followed by hybridisation with sequence-specific oligonucleotides.<sup>35</sup> HCV RNA was extracted by using the QIAamp DSP virus kit in combination with the QIAvac 24 Plus vacuum system (Qiagen GmbH, Hilden, Germany). Probes were bound to a nitrocellulose strip by a poly (T) tail.<sup>36</sup> All laboratory assays were carried out according to the manufacturer's instructions.

### Data Processing and Statistical Analysis

Study data were double entered into Microsoft Excel, cleaned, and validated. The data was exported into IBM SPSS for Windows version 20.0 (IBM Corp, Armonk, NY, USA) for analysis. Descriptive statistics were used to summarise the sociodemographic and behavioural characteristics of study participants. Seroprevalence of HBV and HCV was expressed as a percentage of the entire study population. Chi-square tests and bivariate logistic regression were used to assess associations between dependent and independent variables. Odds ratios were estimated at a 95% confidence interval; statistical significance was set at a *P* value <0.05.

### Ethical Approval

Ethical clearance for the study was obtained from the Institutional Review Board of the College of Medicine and Health Sciences of the University of Rwanda (Reference number 311/ CMHS/2017). Documentation of ethical clearance was presented to research sites administration before starting data collection.

### RESULTS

A total of 220 participants were recruited into the study, of whom 110 were male (50%) and 110 female (50%). The mean age of female and male study participants was 30.26 and 30.24 years, respectively (data not shown). The level of education among participants was generally low: 53.6% had only completed primary education (Table 1). Eighteen per cent of men and 42% of women were unemployed (data not shown).

Two participants (0.9%) including 1 female from Gitare and 1 male from Cyanika had a confirmed HBV infection.



**TABLE 2.** *Continued*

Variables	Participants n	Anti-HCV Detected n (%)	P Value
Ever had tooth extracted			
Yes	27	1 (3.7)	.43
No	193	3 (1.6)	
Ever had surgery			
Yes	17	1 (5.9)	.19
No	203	3 (1.5)	
Ever catheterised			
Yes	19	1 (5.3)	.24
No	201	3 (1.5)	
Ever consumed alcohol			
Yes	83	3 (3.6)	.12
No	137	1 (0.7)	

Four participants (1.8%), including 2 females from Cyanika health centre and 2 males (1 from Gitare and another from Cyanika health centre) had confirmed HCV infection. All HBV and HCV infections were discordant to their respective partners. Two HBsAg positives cases were due to HBV genotype A; all 4 cases of HCV were due to genotypes 4.

In univariate analysis, HCV prevalence varied significantly by occupational group. HCV infection occurred in 12.5% of participants employed in the public sector and 7.7% of participants employed in the private sector, compared to <2% of participants who were self-employed or unemployed (Table 1). HCV infection was significantly associated with scarification (Table 2).

## DISCUSSION

To our knowledge, ours is among the first studies to assess the prevalence and genetic diversity of HBV and HCV among couples attending antenatal care in rural Rwanda. We observed an HBsAg prevalence rate of 0.9% and an anti-HCV prevalence rate of 1.8% among study participants. This corresponds to the World Health Organization's definition of low HBV endemicity.<sup>37</sup> Genotypic analysis of viral types revealed that genotype A represented all confirmed HBV infections, while genotype 4 represented all confirmed HCV infections. No demographic or behavioural factors were associated with

HBV status. However, HCV infection was associated with occupational group and history of scarification.

We compared results of the present study with similar studies, finding that others report substantially higher prevalence rates of HBsAg among non-pregnant adults. Studies from Rwanda report that the prevalence of HBsAg was 2.9% in health care workers<sup>38</sup> and 2.5% in commercial sex workers.<sup>39</sup> Surveys of HIV-infected adults from urban Uganda and Western Kenya report HBsAg prevalence rates of greater than 4%.<sup>40,41</sup> These differences may be explained by the low-risk profile of our study's rural participants, compared to that of population groups known to be at elevated risk of HBV transmission. However, rural status and pregnancy have not consistently been associated with a low risk of HBV. Although in Uganda, polygamous pregnant women had an HBsAg prevalence rate of 0.9%<sup>42</sup>; other studies of pregnant women from rural African settings report HBsAg prevalence rates ranging from 3.8% to 12.7%.<sup>43,44</sup> A study from Kenya reported an HBsAg prevalence rate of 2.1% in adult residents of a rural area.<sup>45</sup>

Reports of HCV prevalence in Rwanda vary markedly. Our finding of an HCV prevalence rate of 1.8% is substantially lower than other surveys conducted in Rwanda, which report HCV prevalence rates of 3.1% in the general population, 4.7% in HIV-infected adults and 9.6% in patients attending Rwanda Military Hospital.<sup>7,21,39,46</sup> However our findings are consistent with the HCV prevalence rates of 1.3% and 1.4% reported in Rwandan health care workers<sup>40</sup> and commercial sex workers,<sup>39</sup> respectively. We conjecture that these variations in HCV infection rates within Rwanda reflect the tendency of HCV to cluster within population subgroups and geographic areas.

We found that all individuals infected with HBV or HCV, were discordant to their respective partners, a finding which has been reported elsewhere. In China, 11.4 % of rural couples who planned to conceive were affected by HBV infection and most of these infections were discordant.<sup>47</sup> Discordance in HBV and HCV infection status may expose seronegative partners to infection, and may be an area where targeted vaccination could be employed. However, numerous large prospective cohort studies did not show an increased risk for HCV transmission among heterosexual discordant couples (married or stable partners), even after 10 or more years of observation.<sup>48</sup>

In our study, all HBV infections were due to HBV genotype A. This is consistent with surveys conducted in Rwandan adults and blood donors, which found the majority of HBV infections in Rwanda were due to genotype A.<sup>6,15</sup> In the East African sub-region, HBV infections have been attributed to a genotypes A, B, C, D, E and H,<sup>44,49-51</sup> but HBV genotypes A and D predominate.<sup>11,52</sup>

In our study, HCV genotype 4 was the only one identified in confirmed HCV infections, which is consistent with a report on hepatitis care referral patients from Rwanda, in whom 96.7% HCV infections were due to HCV genotype 4.<sup>53</sup> A recent phylogenetic analysis of HCV infection in Rwandan blood donors demonstrated the predominance of genotype 4 subtypes 4k, 4q, and 4r, with no geographical difference in their distribution.<sup>54</sup>

We assessed whether sociodemographic and behavioural factors were associated with occurrence of HBV and HCV infection in our cohort. We found that none of the factors evaluated predicted HBsAg seropositivity, but that occupation type was associated with risk of HCV infection, which had the highest frequency in participants employed in the public and private sectors. Our finding that HCV infection was associated with occupation type but not with other factors partly accords with what has previously been reported. Studies from Africa have found that increased risk of HCV infection is associated with X,Y, sharing personal belongings<sup>54</sup> and occupation types that involve exposure related to blood.<sup>55</sup> Our study did not examine occupational activities, so we were unable to assess if the association between HCV infection and occupation type in our cohort was due to occupational exposures to blood or other job-related factors.

## Limitations

This study had several limitations. The small sample size and the low occurrence of HBV and HCV infection in study participants may have reduced the statistical power to detect associations between purported risk factors and infection. Our HBV and HCV genotype analyses were based on a few cases, and, therefore, may not have accurately reflected the general population's genotypic diversity. Finally, study inclusion criteria required that both the male and female partners be enrolled in the study. This may limit the generalisability of study findings to individuals who are in a stable sexual partnership.

## CONCLUSION

Our study revealed low prevalence rates of HBV and HCV in couples attending antenatal clinics in rural Rwanda. Consistent with other data from Rwanda and the sub-region, HBV genotype A and HCV genotype 4, accounted for all confirmed infections. All individuals infected with HBV or HCV were discordant with their respective partners. We recommend that larger studies of HBV and HCV prevalence be conducted in childbearing couples to obtain precise estimates of the prevalence, genetic diversity and risk factors associated with these infections. Such studies will inform targeted preventive measures, especially those aimed at reducing risk among children born to infected mothers.

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