Seroprevalence of Cytomegalovirus among Women of Reproductive Age Attending Selected Hospitals in Zaria Metropolis, Kaduna State, Nigeria.

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Abstract

Background to the Study: Human cytomegalovirus (HCMV) is a member of herpesvirus family. It is the most genetically complex viral pathogen of humans and now the commonest congenital form of infective neurological handicap recognized by the institute of medicine as the leading priority for the developed world in congenital infection. HCMV infection among women of reproductive age especially those that are pregnant can lead to congenital abnormalities and is often associated with serious complications such as microcephaly, mental retardation, deafness and spastic paralysis. This study was done to determine the seroprevalence rate of HCMV infection and its associated risk factors among women of reproductive age in three selected hospitals in Zaria metropolis, Kaduna State. The Cross-sectional study was conducted on 300 consenting women of reproductive age. A structured questionnaire was administered to obtain some demographic data and possible risk factors associated with the infection. The presence of HCMV IgG and IgM specific antibodies were examined in the patients' serum samples using Enzyme Linked Immunosorbent Assay (ELISA) technique. Statistical package for social science (SPSS version 23) was employed to test for the associated risk factors for the infection using the Chi-square test. The result of analysis obtained revealed an overall prevalence of 94.7% (284/300) and 23.9% (88/300) for HCMV IgG and IgM antibodies respectively. The participants' age, nature of occupation, marital status, sexual activities such as-multiple sexual partners and engaging in unprotected sex, were found to be significantly associated with CMV infection among the study population.

Keywords: Cytomegalovirus (CMV), Enzyme Linked Immunosorbent Assay Immunoglobulin G (IgG), Immunoglobulin M (IgM), Risk factors.

INTRODUCTION

Cytomegalovirus (CMV) is a DNA virus that belongs to the viral family known as Herpesviridae or herpesviruses. The species that infect human is typically abbreviated as human cytomegalovirus (HCMV), alternatively known as Human herpes virus5 (HHV-5).Within Herpesviridae, HCMV belongs to the Betaherpesvirinae subfamily, which also includes cytomegaloviruses from other mammals (koichi *et al.*, 2007). It is an enveloped virus, a potential killer or a lifelong silent killer (Hodinka, and Friedman, 2005). CMV infections are common and are usually asymptomatic however, clinically significant infections are encountered frequently in pregnant women, neonates and immune-compromised patients (Brook *et al.*, 2007). HCMV is an important cause of morbidity and mortality among immunosuppressed patients. It is known for producing large cells with nuclear and cytoplasmic inclusions and infects around 40% of the world population (Ryan and Ray, 2004; Offermann and Rosenthal, 2008).

Human cytomegalovirus (HCMV) or human herpes virus 5 is one of the major causes of congenital infections (Munro *et al.*, 2005; Kenneson and Cannon, 2007; Dollard *et al.*, 2007; Cannon, 2009; Sotoodeh *et al.*, 2010). Its clinical manifestations range from asymptomatic forms (90% of cases) to severe fetal damage, and in rare cases, death due to miscarriage. Furthermore, 10 to 15% of the children who are asymptomatic at birth may develop late sequelae, especially hearing defects, after a period of months or even years (Massimo *et al.*, 2009).

HCMV can be transmitted via infected saliva, sexual contact, placental transfer, breast feeding, blood transfusion and solid-organ transplantation (Bowden, 1991). Latency following a primary infection may be punctuated by periodic reactivations that give rise to recurrent infections, and *in utero* transmission may occur during either primary or recurrent infections. Although the mechanisms and the pathogenesis of intrauterine transmission and severe fetal infection in the presence of preexisting maternal immunity are unknown, an analysis of CMV strain-specific antibody responses revealed an association between intrauterine transmission of CMV and reinfection with new or different virus strains in seroimmune women (Boppana *et al.,* 2001), but it is likely that most recurrent infections are due to reinfection.

The risk of congenital infection is much higher during primary infection (Fowler and Boppana, 2006). It has been reported that the risk of fetal damage is greater if the primary infection occurs during the first trimester of pregnancy (Adler and Marshall, 2007).

CMV is a slow replicating virus from the herpes family, infecting only as many as 1% of all neonates in developed countries, but demonstrating up to 90% IgG-positivity in developing countries (Cannon *et al.,* 2010). As well as increasing with age, CMV seroprevalence may also depend on sexual activity and occupation, particularly occupations involving close contacts with children in a community setting. In the case of parents, contact with the urine or saliva of their children is a major source of infection (Adler, 1991).

Materials and Methods

3.1 Study area and population

This study was conducted in Zaria metropolis, Kaduna state, Nigeria. Kaduna state lies between latitude 09^0 2'N and 11^0 23' N and longitude the 06^0 15 'E and 08^0 60'E and shares boundaries with Katsina, Kano and Zamfara states to the north, Plateau and Bauchi State to the east, Nasarawa State and Federal Capital Territory to the south and Niger to the west. The state consist of 23 Local Government Areas and is divided in to three senatorial districts.

3.2 Study Population

The study population comprised of women of reproductive age attending selected hospitals in Zaria metropolis Kaduna State. The hospitals were Major Ibrahim B. Abdullahi Memorial Hospital (MIAMH) Sabon-gari Zaria, Hajia Gambo Sawaba Hospital (HGSH), Zaria and University Health Services A.B U Zaria.

3.3 Inclusion Criteria

This will include all women of reproductive age attending the selected hospitals within the study period and gave their consent to the study.

3.4 Exclusion Criteria

Women below reproductive age, women that have reach menopause age and women of reproductive age who did not consent to the interview were not involved in this study.

3.5 Ethical Approval and Consent

Ethical approval to carry out this research work was obtained from the Ministry of Health, Kaduna State and the ethical committee of various hospitals involved. The purpose and procedure of the study was explained to all participants and their consent was sort.

3.6 Data Collection

Questionnaires having information on socio-demographic factors such as age, marital status, as well as risk factors such as level of education, occupation, geographic location ,history of blood transfusion and other risk factors that may be associated with cytomegalovirus were recorded.

3.7 Sample Collection

About 5ml of venous blood was collected from each patients aseptically by venipuncture and dispensed into sterile labeled anticoagulant free containers, followed by centrifugation at 2500rpm for 5minutes to separate the serum for the detection of CMV specific antibodies; Immunoglobulin M and Immunoglobulin G. The sera samples were then transferred into sterile properly labeled screw capped vials and stored at -20^{o}C until required for analysis.

3.8 Laboratory Diagnosis

Enzyme-linked immunosorbent Assay (Diagnostic Automation, inc., Calabasa USA) technique was used to assess the presence of CMV IgG and IgM in sera samples obtained from the participants in the study.

3.9 Statistical analysis

Data and results obtained from this study were analyzed using the statistical package for social sciences (SPSS version 21). Chi-square analysis was done to determine the level of association between variables and CMV infection at 95% confidence interval (CI) and P-values that are less than 0.05 were considered to be statistically significant.

Results

A total of Three hundred (300) blood samples were collected from consenting patients (women of reproductive age) attending three different hospitals within Zaria metropolis. One hundred (100) samples were collected from each of the hospitals enrolled in this study namely; University health services of Ahmadu Bello University Zaria (UHS), Hajia Gambo Sawaba General Hospital (HGSH) and Major Ibrahim B. Abdullahi. All samples collected were tested for the presence of Cytomegalovirus (CMV) IgM and IgG antibodies. A total of 88 (29.3%) and 284 (94.7%) patients were positive for CMV-IgM and IgG respectively (Figure 1).

Presented on (Table 1) is the analysis of data showing the level association between the prevalence of CMV-infection and some demographic characteristics among women of reproductive age. All participants enrolled in this study were grouped according to their age, of which 53, 154, 66, and 27 of the patients fall within the age-group 11-20, 21-30, 31-40 and 41-50 respectively. The analysis of result according to age showed that patients within age group 21-30 had the highest prevalence of 39.0% (60/154) for CMV-IgM and the highest sero-prevalence of 96.7% (64/66) for CMV-IgG was recorded among those within age group 31-40, while the least prevalence of 14.8% (4/27) and 86.7% (46/53) was observed among patients within age-group 41-50 and 11-20 for CMV-IgM and IgG respectively. There was a significant association between age and CMV-IgM ($p=0.008$), however, CMV-IgG reflects no significant association among the age groups. The subjects were grouped into four major categories based on their marital status response; 158 responded to be married, 109 were single, 6 were divorced and 15 were widow, however, 12 (out of the patients) gave no response. The analysis of result based on marital status, showed that, the highest prevalence of 66.7% (4/6) for CMV-IgM was recorded among the divorced patients, while the highest prevalence of 100% for CMV-IgG sero-positivity was recorded among the divorced (6/6) and the widow (15/15). However, only CMV-IgM had a significant association with the patients' marital status ($p=0.038$).Analysis of data obtained in this research according to highest level of patients' education attained, the result showed that Cytomegalovirus IgM sero-positivity was highest among women with secondary school level of education with a percentage prevalence of 36.6% (30/82), while the highest sero-positivity for CMV-IgG was recorded among those with tertiary level of education with percentage prevalence of 97.5% (117/120). There was no significant association between prevalence of CMV infection with respect to patients' educational status. In relation to Occupation, the patients were group into six (6) different categories based on their occupation; 43 were Civil servant, 3 were artisan, 48 were trader, 6 were farmers, 39 were unemployed, 129 were student and 32 gave no response. The highest prevalence of 66.7% (2/3) of CMV-IgM antibody was observed among patients that were artisan while the highest prevalence of 100.0% for CMV-IgG antibody was observed among those that were artisan and farmer. The difference observed was significant for CMV-IgM ($p<0.05$).

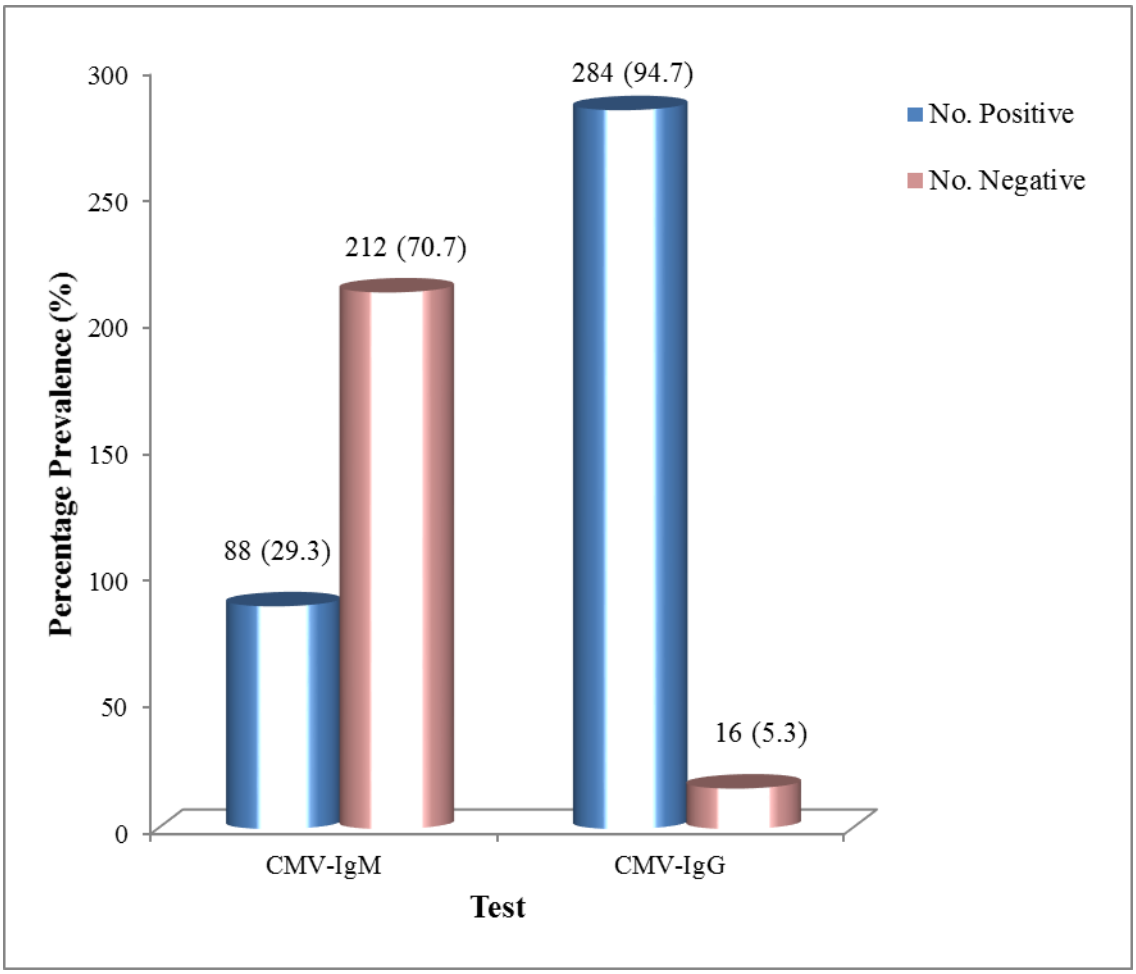

Figure 1: Overall Prevalence of CMV-IgM and IgG antibodies among the study population

Key: CMV= Cytomegalovirus, IgM= Immunoglobulin M, IgG= Immunoglobulin G, No=Number, %= Percentage.

Table 1: Association between Demographic Characteristics and CMV Infection among Women of Reproductive Age

Variables	Number Examined	CMV-IgM			CMV-IgG		
		Positive n (%)	χ^2	P- value	Positive n (%)	χ^2	P- value
Age (Years)							
11-20	53	8(15.1)			46(86.7)		
21-30	154	60(39.0)	13.318	0.008*	148(96.1)	3.782	0.436

31-40	66	16(24.2)			64(96.7)		
41-50	27	4(14.8)			26(96.3)		
Marital status							
Married	158	53(33.5)			150(52.7)		
Single	109	20(18.3)	12.359	0.038*	103(94.5)	4.265	0.371
Divorced	6	4(66.7)			6(100)		
Widow	15	7(46.7)			15(100)		
No response	12	4(33.3)			10(3.5)		
Educational Status							
Primary	29	8(27.6)			27(93.1)		
Secondary	82	30(36.6)			77(93.9)	7.709	0.103
Tertiary	120	26(21.7)	6.578	0.160	117(97.5)		
Informal	36	13(36.1)			31(86.1)		
No response	33	11(33.3)			32(97.0)		
Occupation							
Civil servant	43	12(27.9)			42(97.7)		
Artisan	3	2(66.7)	18.574	0.045*	3(100)	7.135	0.319
Trader	48	19(39.6)			46(95.8)		
Farmer	6	2(33.3)			6(100)		
Unemployed	39	16(41.0)			34(87.2)		
Student	129	28(21.7)			124(96.1)		
No response	32	9(28.1)			29(81.3)		
Total	**300**	**88(29.3)**			**284 (94.7)**		

Key: χ^2 =Chi-square, %= prevalence *=Significant association exist as p<0.05, n = number

History of sexual activity (as regards; number of sexual partners, participating in unprotected sex), pregnancy and number of children among the women enrolled in this study were also considered as a possible risk factor for CMV infection (Table 2).

Based on number of sexual partners, sixty (60) out of the 300 women enrolled in this study declined being sexually active. The highest prevalence of 50.0% (10/20) for CMV-IgM was recorded among those who admitted to having multiple sexual partners while the lowest prevalence of 22.9% (40/175) was recorded among those who had one sexual partner. For CMV-IgG those who had just one sexual partner recorded the highest prevalence of 96.0% (168/175) while the least prevalence was recorded among those who had multiple sexual partners. However, the result of analysis based on this factor, showed only CMV-IgM to be statistically significant with number of sexual partners as a risk factor for CMV infection (χ^2=13.489, p=0.004).

Further analysis to examine involvement of subjects in unprotected sex as a risk factor for CMV infection among the remaining 240 women who admitted to be sexually active revealed that, those who admitted to, participating in unprotected sex had a higher prevalence of 35.9% (33/92) and 98.9% (91/92) compared to 19.6% (29/148) and 93.2% (138/148) for CMV-IgM and IgG respectively among those who had protected sex. The differences observed were found to be statistically significant for both CMV-IgM and IgG (p>0.05).

Based on pregnancy status, only eighty-six 86 out of the 300 women in this study were pregnant. Analysis of result showed a higher prevalence of 41.9% (36/86) and 97.7% (84/86) for CMV-IgM and CMV-IgG respectively among the pregnant women as against 24.3% (52/214) and 93.5% (200/214) among the non-pregnant women. However, pregnancy as a risk factor was found to significantly associated with CMV-IgM alone (p<0.05).

Analysis of result based on number of children shows that there was no significant difference between CMV-infection and number of children (p>0.05). The highest prevalence for CMV-IgM sero-positivity of 100% (1/1) was recorded among those who had seven or more children; however prevalence of 100% was recorded for CMV-IgG among those who had three or more children.

Data obtained in this study were also analysed to examine the level of association between CMV and HIV infection. Out of 300 subjects enrolled in this study, 11 were positive for HIV infection. Higher prevalence of 45.5% (5/11) was recorded for CMV-IgM among those who were positive for HIV infection. However, those who were negative for HIV infection recorded a higher percentage prevalence of 95.2% (275/289) for CMV-IgG. The difference observed were not statistically significant (p>0.05).

The presence of other sexually transmitted diseases was also examined as a possible risk factor for CMV-infection. The result of analysis showed that those that had sexually transmitted disease recorded a lower prevalence of 13.6% and 15.8% as compared to 78.4% and 75.7% for CMV-IgM and IgG respectively, among those who did not have. The association between CMV-IgM and CMV-IgG antibodies and sexually transmitted disease was not statistically significant (p>0.05).

Analysis of prevalence obtained based on blood transfusion in this study showed that there was no significant association between transfusion and CMV-infection (p>0.05). However, higher prevalence of 30.8% (12/39) was recorded among women who had previously undergone transfusion for CMV-IgM, whereas, those who have never been transfused, recorded a higher prevalence of 95.4% (249/261) for CMV-IgG.

Table 2: Association between CMV Infection and Some Risk Factors among Women of Reproductive Age

Risk Factors	No Tested	CMV-IgM			CMV-IgG		
		Positive n (%)	χ^2	P- value	Positive n (%)	χ^2	P- value
No of sexual partners							
None	60	26(43.3)			55(91.7)		
One	175	40(22.9)	13.489	0.004*	168(96.0)	2.619	0.454
Two	45	12(26.7)			43(95.6)		
Multiple	20	10(50.0)			18(90.0)		
Unprotected Sex							
Yes	92	33(35.9)			91(98.9)		
No	148	29(19.6)	7.843	0.005*	138(93.2)	4.170	0.041*
Sub Total	**240**	**62(25.8)**			**229(95.4)**		
Pregnant							
Yes	86	36(41.9)			84(97.7)		
No	214	52(24.3)	9.127	0.003*	200(93.5)	2.160	0.142
Number of children							
None	257	76(29.6)			243(94.6)		
1-2	22	8(36.4)	0.439	0.932	20(90.9)	1.673	0.643
3-4	17	2(11.8)			17 (100.0)		
5-6	3	1(33.3)			3(100.0)		
≥7	1	1(100)			1(100.0)		

Total	**300**	**88(29.3)**	**284 (94.7)**

Key: χ^2 =Chi-square, %= prevalence *=Significant association exist as p<0.05, n= number

Table 3: Association between CMV Infection with respect to HIV and STD Status.

Risk Factors	No Tested	CMV-IgM			CMV-IgG		
		Positive n (%)	χ^2	P- value	Positive n (%)	χ^2	P- value
HIV STATUS							
Positive	11	5(45.5)			9(81.8)		
Negative	289	83(28.7)	1.432	0.231	275(95.2)	3.734	0.053
STD							
Yes	46	12(13.6)			45(15.8)		
No	230	69(78.4)	0.284	0.868	215(75.7)	2.905	0.234
No response	24	7(8.0)			24(8.5)		
Blood Transfusion							
Yes	39	12(30.8)			35(89.7)		
No	261	73(29.1)	0.045	0.851	249(95.4)	2.152	0.142
Total	**300**	**88(29.3)**			**284 (94.7)**		

Key: χ^2 =Chi-square, %= prevalence *=Significant association exist as p<0.05

Discussion

Findings in this study revealed that the prevalence of HCMV in women of reproductive age in Zaria metropolis, Kaduna state is high. An overall prevalence of 94.7% was observed for CMV-IgG antibodies while 29.3% was recorded for CMV-IgM antibodies representing those that had acute infection of CMV among the study population. The lower prevalence of 29.3% for IgM antibodies observed in this study is possibly due to the fact that majority of the women must have recovered from primary infection with the loss of CMV IgM antibodies by the time they reach the reproductive age (Griffths *et al.*, 2001, Fowler *et al.*, 2003). However, according to Khairi *et al.* (2013), CMV-IgG antibodies on the other hand, remain in the body of an individual for life after previous infection and protects considerably against subsequent infection. Hence, the detection of CMV-IgG in this study indicates that the women had previously been infected with CMV and negative results of CMV-IgG test means that the women have not been infected with the virus.

When compared to other findings within Nigeria; the prevalence of 94.7% recorded in this study was similar to 94.8% previously reported by Yero *et al.* (2014) in Kaduna State and slightly lower than 97.2% reported in Lagos by Ahmad *et al.* (2011) and 98.7% reported in Sokoto State by Akinbami *et al.* (2011). Similar seroprevalence had also been reported within the continent of African; Kafi *et al.* (2009) reported a prevalence 95% in Sudan and a prevalence of 96% was reported by EL- Nawawy *et al.* (1996) in Egypt. However, the result of this study were higher than 46.8% reported by picone *et al.* (2009) in France and that of Sharas *et al.* who reported a prevalence of 60% in the United State in 2006. The high CMV-IgG seroprevalence observed in this study was seen to be similar to that reported in other developing countries, whereas, it was higher than those reported in the developed countries. This may be attributed to the depreciating socioeconomic status, low standard of education, poor hygienic practices among these women and inadequate health care facilities which may play important roles in increasing the rate of CMV transmission in developing countries (Staras *et a*l., 1994; Yero *et al.,* 2014).

The prevalence rate of CMV IgM sero-positivity (29.3%) recorded among the women in this study was far higher than 1.7% reported in Korea by Seo *et al.* (2009), 2.5% reported by Hamdan *et al.* (2011) in Western Sudan, 7.2% in Malaysia by Saraswathy *et al.* (2011) and 13% in Poland by Gaj *et al.* (2012).

Analysis of prevalence of CMV infection with respect to age revealed no specific pattern, however, there was a significant association between the age group and prevalence of CMV-IgM antibodies (χ^2=13.318, p=0.008), with the highest prevalence of 39.0% being recorded among women within the age group 21-30 years. The rise in CMV-IgM sero-positivity within this age group may not be unconnected to the increase in sexual activity due to realization of sexual maturity leading to high level of sexual promiscuity, hence increase in transmission rate of the infection (Griffthis *et al.,* 2011). Whereas, the lowest prevalence of 14.8% recorded among those within age group 40-50 years. May likely be attributed to the waning nature of CMV-IgM as majority of the women previously exposed to the infection must have recovered from primary infection over time (Saidu *et al*., 2015).

Seroprevalence of CMV infection based on marital status among the women revealed a significant association for CMV-IgM antibodies. The peak of prevalence was recorded within the divorced women group. The reason for high prevalence in these group of women might be due to the fact that they are more exposed to new infection due to multiple sexual partners. This is in agreement with the report of Tremlog *et al.* (2009), who reported sexual exploitation as a factor for transmission of CMV infection.

In this study, the distribution of seroprevalence of CMV infection among women of reproductive age by educational status showed no significant association. Although, women with secondary school education had the highest prevalence for CMV IgM antibodies. This might be as a result of the fact that those women in these groups are more exposed sexually than those in primary schools. This result contradict the earlier report of Yero *et al*. (2014) who reported that seroprevalence rate of CMV decrease with increase in level of education.

Analysis of CMV infection based on occupation shows that there was significant association in relation to occupation by CMV IgM antibodies. The highest prevalence of CMV was observed among patients that were artisan for both IgG and IgM antibodies this may be as a result of the nature of their work which involve frequent contact with different people which could possibly lead to high transmission rate of CMV infection among these subjects. This does not agree with previous study of Bate *et al.* (2010).

The result of analysis of those women who engage on unprotected sex show significance association with CMV IgM and IgG antibodies with highest prevalence in those women who engaged in unprotected sex. Number of sexual partners were also significant for IgM with highest prevalence in those women who had multiple sexual partners. A greater number of sexual partner did increase risk of transmission of CMV. Increased sexual exposure identifies those who engaged in more or perhaps riskier behaviour or selects individual who are exposed to different partner pool are at high risk of transmitting CMV infection (Ray, 1997).

Pregnancy was found to be significantly associated with CMV infection with higher prevalence for both IgG and IgM antibodies among the pregnant women than those women that are not pregnant. This report contradicts the report of Yero *et al.* (2014), who observed no significant association between pregnancy and CMV infection. The reason for high prevalence of CMV infection among the pregnant women in Zaria metropolis may be as a result of the fact that pregnancy has been reported as a stressor on women and could lead to primary exposure or cause reactivation of the virus from its latent state. This agrees with the report of Biswas *et al.* (2011). Hence the high prevalence of CMV infection among pregnant women implies that there might be a corresponding high incidence of congenital CMV infection among infants born in the area (Mussi – Pinhata *et al.*, 2009).

This study revealed no significant association between number of children and CMV prevalence among the women tested for both CMV IgG and IgM. It was observed that women with seven or more children had the highest CMV IgM sero prevalence while 100% of CMV IgG seroprevalence was recorded among those women who had three or more children. This might be as a result of the women acquisition of the infection from their young children as this agrees with the report of Adler (2004), who reported the exposure to young children as a factor for transmission of CMV infection.

HIV tested and HIV status, were also found not significantly associated with CMV prevalence in this study, however those that are HIV positive had the highest prevalence for IgM antibodies while those tested negative had the highest prevalence by IgG antibodies. The highest prevalence for CMV IgM antibodies among those women that are HIV positive might be as a result of their state of immunosuppression and thus may increase the risk of acquiring new infection.

History of sexually transmitted disease was also not found significant for both IgG and IgM antibodies. Having unprotected sex increase the rate of transmission of CMV, although those that has the history of STD had the highest prevalence for IgG antibodies but lowest prevalence for IgM compare to those that has the history of STD.

Further analysis to evaluate risk factors that are associated with CMV infection in this study revealed no significant association with participants' history of blood transfusion. This disagrees with the findings of Matos *et al.* (2010), who reported blood transfusion as a risk factor for transmission of CMV infection. The reason for the disagreement here could be as a result of the disproportionate size of women who were transfused to those who were not transfused. However, highest prevalence rate was recorded among women who had previously undergone transfusion for CMV-IgM, whereas, a higher prevalence rate for CMV-IgG was recorded among those who had never been transfused (Matos *et al.*, 2010).

Conclusion

In conclusion, this study showed that CMV infection is widespread among women of reproductive age in Zaria metropolis with prevalence of 94.7% and at 29.3% for CMV IgG and IgM antibodies respectively. The high prevalence was attributable to age, nature of occupation, marital status, participating in unprotected sex and multiple number of sexual partners. It is recommended that attempts to control the transmission of CMV infection through the risk factors implicated in this study should be adopted.

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