Review Article

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Archives of Clinical Microbiology
1989-8436

2023
Vol. 14 No. 3: 234

A Review on Molecular Epidemiology of *Cytomegalovirus* in Northern Nigeria

Timothy Waje*, Iliyasu MY, Ahmed Faruk Umar, Ediga B Agbo

Microbiology in Biological Sciences, Abubakar Tafawa Balewa University, P.M.B. 0248, Bauchi, Nigeria

Corresponding author: Timothy Waje

wajetim@yahoo.com

Tel: +2348086527453

Microbiology in Biological Sciences, Abubakar Tafawa Balewa University, P.M.B. 0248, Bauchi, Nigeria

Citation: Waje T, Iliyasu MY, Umar AF, Agbo EB, (2023) A Review on Molecular Epidemiology of Cytomegalovirus in Northern Nigeria. Arch Clinic Microbio, Vol. 14 No. 3: 234.

Abstract

Background: *Cytomegalovirus,* also known as "*Human Cytomegalovirus"* infects people of all ages. The virus derives its name from its ability to cause cell enlargement, Cyto means cell, while megalo means enlargement. It shares a common characteristic of lifelong latency with other members of *Herpesviridae* such as: *Epstein Bar Virus, Varicella Zoster Virus, Herpes simplex 1 and 2,* and *Kaposi Sarcoma Herpes Virus.* These are associated with several illnesses such as oral and genital blisters, congenital disorders, encephalitis, and Kaposi Sarcoma, among others. The virus poses a significant threat to public health worldwide, especially due to its latency and absence of effective medical treatment despite self-limitation.

Methodology: This review covers a systematic review, meta-analysis, and scoping review on *cytomegalovirus* with a view to assess the viral burden among the studied populations and identify reported states within Northern Nigeria endemic with the virus. The review also identified active infections and effect of the virus on the reported people.

Results: Active infections with *Cytomegalovirus* have been reported among pregnant women in Kebbi State (IgM 1.10%), IgM of 57.90% among blood donors, and 7.10% in HIV patients in Sokoto State, 14.40% IgM among HIV patients with retinitis in Kano, and 11.40%, among HIV patients, 10.50% in Pregnant women and 23.90% among women of reproductive age respectively, in Kaduna State all in Northwest Nigeria. Similarly, in the North, Central active infections were reported in Benue (3.50%) among pregnant women, 19.80% among HIV patients in Bida, and 2.60% among blood donors in Niger State, 24.90% among pregnant women in Kwara State, 21.70% among pregnant women in Kogi State, 10.60% in HIV Children and adolescent in the FCT Abuja, 9.50% among recurrent miscarriage women as well as 4.80% in normal women in Plateau State respectively. *Cytomegalovirus* decreases CD4 counts among HIV Patients, causes miscarriages among pregnant women, retinitis in HIV patients, and renders blood ineligible for Donation. Therefore, regular medical checkup and treatment of infected cases to prevent complications are recommended.

Keywords: Prevalence; Nigeria; Molecular; Epidemiology

Received: 04-Mar-2022, Manuscript No. ipacm-23-13558; **Editor assigned:** 06-Mar-2023, Pre-QC No. ipacm-23-13558 (PQ); **Reviewed:** 15-Mar-2023, QC No. ipacm-23-13558; **Revised:** 24-Mar-2023, Manuscript No. ipacm-23-13558 (R); **Published:** 29-Mar-2023, DOI: 10.36648/1989-8436X.22.14.03.234

Introduction

Cytomegalovirus, commonly known as CMV, is an enveloped virus with a double-stranded complex DNA molecule that encodes over 200 viral proteins and belongs to a family of viruses called *Herpesviridae* and *Betaherpesvirinae* subfamily [1, 2]. Moreover called "*Human Cytomegalovirus (HCMV)*", it infects people of all ages and has a similar characteristic of lifelong latency to other members of the family such as: *Epstein Bar Virus, Varicella Zoster Virus, Herpes simplex 1 and 2* and *Kaposi Sarcoma Herpes*

Virus (KSHV), among others [3]. Members of the family cause a variety of diseases including oral and genital blisters, congenital disorders, encephalitis, and Kaposi Sarcoma [4]. *Cytomegalovirus* shares the subfamily "*Betaherpesvirina*e" with *Muromegalavirus* (infects Mice and rats)*, Proboscis virus* (causes acute hemorrhagic disease in elephants)*, Quwivirus* (guinea pigs and bats as hosts), and *Roseolovirus* (Mammals as host, infects T lymphocytes in humans) [5, 6]. The *Human Cytomegalovirus* is spherical in shape with a double-stranded linear DNA in an icosahedral capsid surrounded by a lipid bilayer enveloped which composed of various glycoproteins such as glycoprotein B (gB), gN, gH, gM, gO, gL, and gN useful in cell attachment and penetration [7, 8] (**Figure 1**).

Like other viruses, the life cycle of *cytomegalovirus* begins with the virion attachment to the host cells via interaction of viral envelope glycoproteins (gH, gN, gO, etc.) with host cell surface receptors delivering the capsid and tegument proteins into the cell. The capsid migrates to the nucleus where the viral genome is freed. The tegument proteins regulate host response as well as genome replication in the order of early and immediate (IE 1) gene expression, delayed early (IE 2) gene expression, and late gene expression, respectively. The late gene expression initiates capsid assembly in the nucleus, which associates with the tegument proteins and migrates to the viral assembly complex where they acquire further tegument and envelope (virions encapsulation of replicated DNA as capsids) .These migrate to the cytoplasm where secondary development occurs at the Endoplasmic Reticulum and Golgi Apparatus before being release together with dense non-infectious agents by exocytosis [9, 10] (**Figure 2**).

Genetic diversity has been reported in *Cytomegalovirus* through genotyping of the viral glycoproteins gB1, gN4AN1, gB3, gH2, gB2, gB4,) from PCR positive clinical samples (urine, saliva, and plasma) producing gB2, gN3BN1, gB1, 2, 4, gH1, gB1, gB2 subtypes among others[11]. The diversity in viral glycoproteins plays a great role in viral tropism and spread [12]. Mutated genes such as *UL9, UL1, RL6, RL5A*, and *US*9 due to deletions and insertions in *Cytomegalovirus* genome have been reported with shared ancestral features [13]. Virulence genes such as *UL55* (codes for gB for attachment) and *US9* (codes gpUS9 cell-to--to-cell spread in epithelia cells) play a key role in virus tropism while *UL8*3 (codes for matrix protein, inhibits antigen processing of 72-kDa IE protein), *US3* (gp32/33, retains Major Histocompatibility Complex(MHC) class 1 molecules loaded with peptides in Endoplasmic Reticulum ER) and US2/ US11 (gp24/gp33, directs detained MHC class 1 molecules from ER to proteasome for degradation) are genes that enable the virus to evade the host immunity [14].

The *Human Cytomegalovirus* is described as the most successful human viral pathogen due to its transmission routes which are utero-perinatal and postnatal with the ability to remain latentin the host for a very long time without evoking clinical signs and symptoms [12]. It can be activated by critical illness, drugs, inflammatory and stress mediators, immunosuppression, organ transfer, among other factors [15]. The virus has been reported among women within child bearing age posing a significant risk for perinatal or neonatal transmission [16; 17]. The common mode of transmission of the virus is through direct contact of soft tissues or open sores with body fluids of infected persons such as blood, tears, urine, breast milk, semen, saliva, and infant contact with the mother's genital secretions during birth [18]. The virus spreads within an individual causing multi-systemic effect involving many tissues and organs such as lungs, liver, eye (retina), muscles, brain, and gut among others [10]. Although latency results in asymptomatic infections, viral activation leads to symptoms such as fever, encephalitis (brain

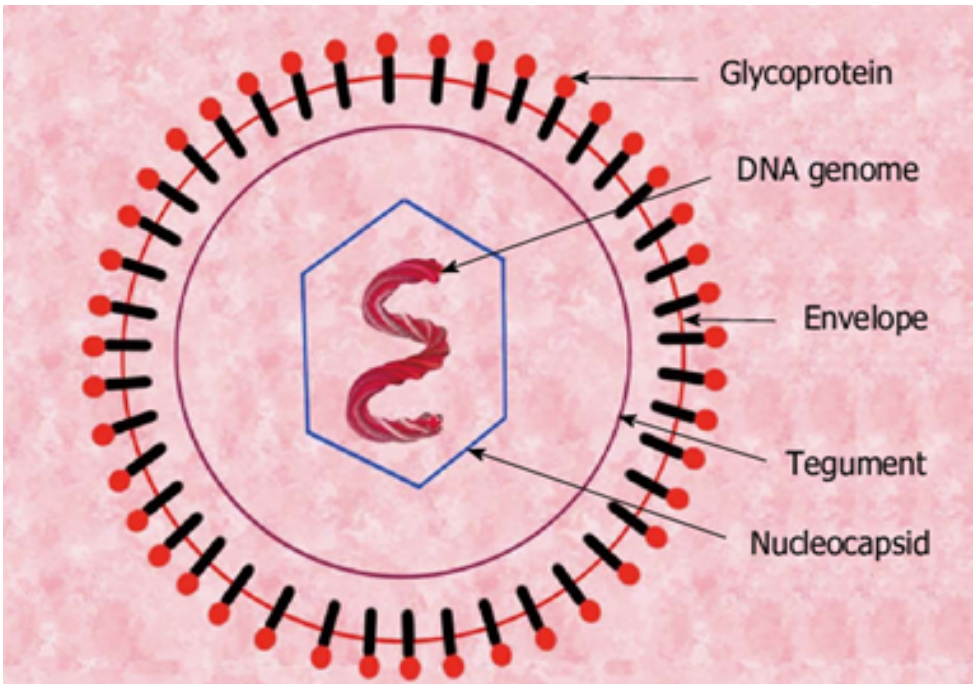

Figure 1 The Structure of *Human Cytomegalovirus.*

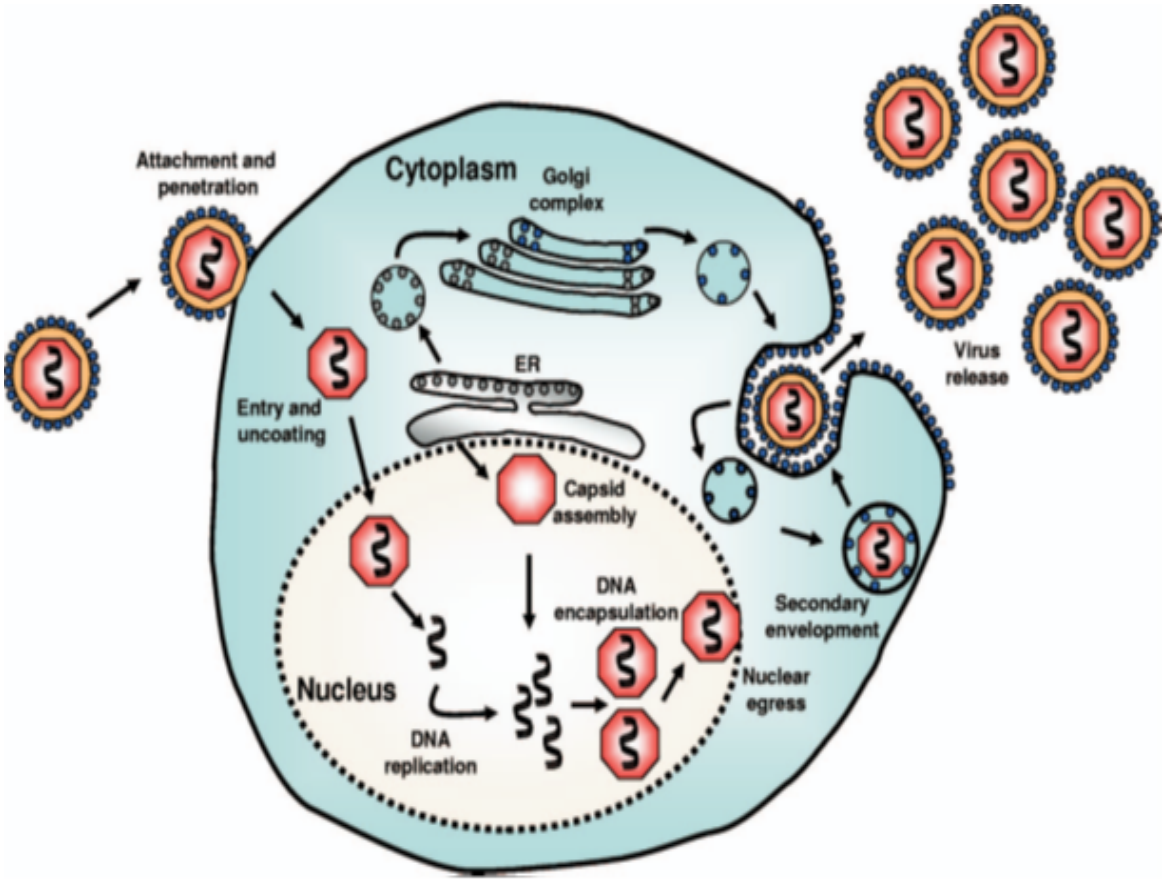

Figure 2 The Life Cycle of Cytomegalovirus.

inflammation) causing seizures and coma, pneumonia with hypoxemia, liver inflammation (hepatitis), large ulcers, shortness of breath, and vision problems. *Cytomegalovirus* can cause sore throat, fatigue, hepatitis, mononucleosis, and swollen glands [3]. Complications can result from gastrointestinal problems (diarrhea, colon inflammation, abdominal pain, and blood in the stool), pneumonitis, and inflammation of the brain (encephalitis), and liver problems [20]. Immunocompromised persons such as HIV patients and organ transplant recipients are at serious risk for *Cytomegalovirus* contraction [21]. Infected pregnant women pass the virus to either the unborn child in the womb via blood circulation or through contact of the baby with genital secretions during delivery [22]. *Cytomegalovirus* can be diagnosed in the laboratory by the following ways:

1. Serologic investigations for IgM in active infection and IgG due to a previous exposure/recovery.
2. Detection of viral antigen or DNA using Polymerase Chain Reaction (PCR).
3. Culture of urine samples particularly in infants.
4. Biopsy in immunocompromised patients [21].

Cytomegalovirus infection is self-limiting with occasional recovery without medication, especially in adults, but medications (antivirals) can be administered to children and adults with weak immunity to slow viral replication [23]. Although Ganciclovoir may have adverse effects, it reduces viral spread in those with congenital or recurring *CMV* infections, so organ damage may require hospitalization [20]. *Cytomegalovirus* is a public health concern globally [3, 24, 25]. Therefore, this paper involves a systematic review, meta-analysis, and scoping review with the aim of investigating the molecular epidemiology of *cytomegalovirus* in Northern Nigeria.

Epidemiology of *Human Cytomegalovirus*

Epidemiology is the study of the distribution (frequency and pattern) and determinants in relation to causes and risk factors for health-related issues and diseases in a specified population with application for prevention and control [26]. Several factors are involved in the epidemiology of *Human Cytomegalovirus.* Although the virus is highly prevalent globally, its prevalence has a direct correlation with socio-economic status and advance age [27]. Organ recipients, persons with weakened immunity, and those on immunosuppressive drugs are at a high risk of *CMV* contraction [28]. A *CMV* prevalence of 94.50% was reported among persons with platelet disorders, 83.30% in those with anemia and leukemia, and 91.00% in a cross-sectional study among patients with hematological diseases in the Western Brazilian Amazon [29]. A high prevalence of the virus has been reported in developing countries where the socio-economic status are low compared to Europe, some parts of Australia, and North America with low prevalence [30]. *Human*

Cytomegalovirus Immunoglobulin G (IgG) prevalence of 39.30% and 48.0% was reported among adult men in France and United States, respectively, but among women of reproductive age this was 45.60%-95.70% (Europe), 60.20% (Japan), 58.30%-94.50% (LATAM), and 24.60%-81.0% (North America) [31]. Maternal and congenital *CMV* Seroprevalence of 98.1% and 8.4%, respectively, was reported among mothers and infants in Columbia [32]. Genetic variability in *Human Cytomegalovirus* has been described as complex and enables the virus access to multiple hosts with the ability to thrive well even in unfavorable conditions [33; 34]. This diversity in *Human Cytomegaloviruses* has been linked to changes in the envelope glycoproteins (gM, gO. gN, gH, etc) producing subtypes [11]. Polymorphism (variants) of *HCMV* was reported in UL54 (P342S, S384F, K434R, S673F, T754M, R778H, C814S, M827I, G878E, S880L, E888K and S976N) and in UL97 (M615T) among DNAemia patients in Taiwan [35]. In a Phylogenetic analysis of UL146, UL144, and UL55 genes, distinct strains of *HCMV* were reported among different families [36].

In Africa, *Human Cytomegalovirus* is a common etiologic agent of congenital infections in children as well as pneumonia and meningitis, particularly among immunosuppressed hospitalized patients [37]. The endemicity has been described high in young infants 18 months of age with a prevalence rate of 83.00% in Zambia while in Nigeria high prevalence among prospective blood donors was significantly associated with overcrowding [38;39]. The progression in the burden of HIV in Africa with its increasing morbidity and mortality has been associated with the effect of *Human Cytomegalovirus* either as a secondary pathogen or co-pathogen with HIV exerting a concerted effects against the immune system of their host with a consequent inflammatory effects [40].

Human Cytomegalovirus in Nigeria

Nigeria consists of 36 states and the Federal Capital Territory (FCT) distributed in six geopolitical zones such as North West, North East, North Central, South-South, South West and South East respectively. Northern Nigeria is made up of three geopolitical zones which include: North West, North East and North Central also known as Middle Belt [41; 42](**Figure 3**).

There have been several reports on the prevalence of *Human Cytomegalovirus* in Nigeria. Anti-*HCMV* IgG prevalence rate of 86.00% and 13.20% for IgM among HIV patients with 72.00% IgG and 2.80%IgG in HIV negative persons have been reported in Nigeria [43]. A prevalence rate of 3.80% was reported among infants in Lagos through Polymerase Chain Reaction with two positive symptomatic subjects with liver and spleen enlargement and pneumonia related illness [44]. Furthermore, a Seroprevalence of 97.2% of IgG against *Cytomegalovirus* was reported among normal pregnant women in Lagos, Nigeria [45]. In a related study,a prevalence of 60.00% IgG to the virus was reported among pregnant women in Oshogbo Ogun State [30]. In Abakaliki Ebonyi State, a *HCMV* infection prevalence of

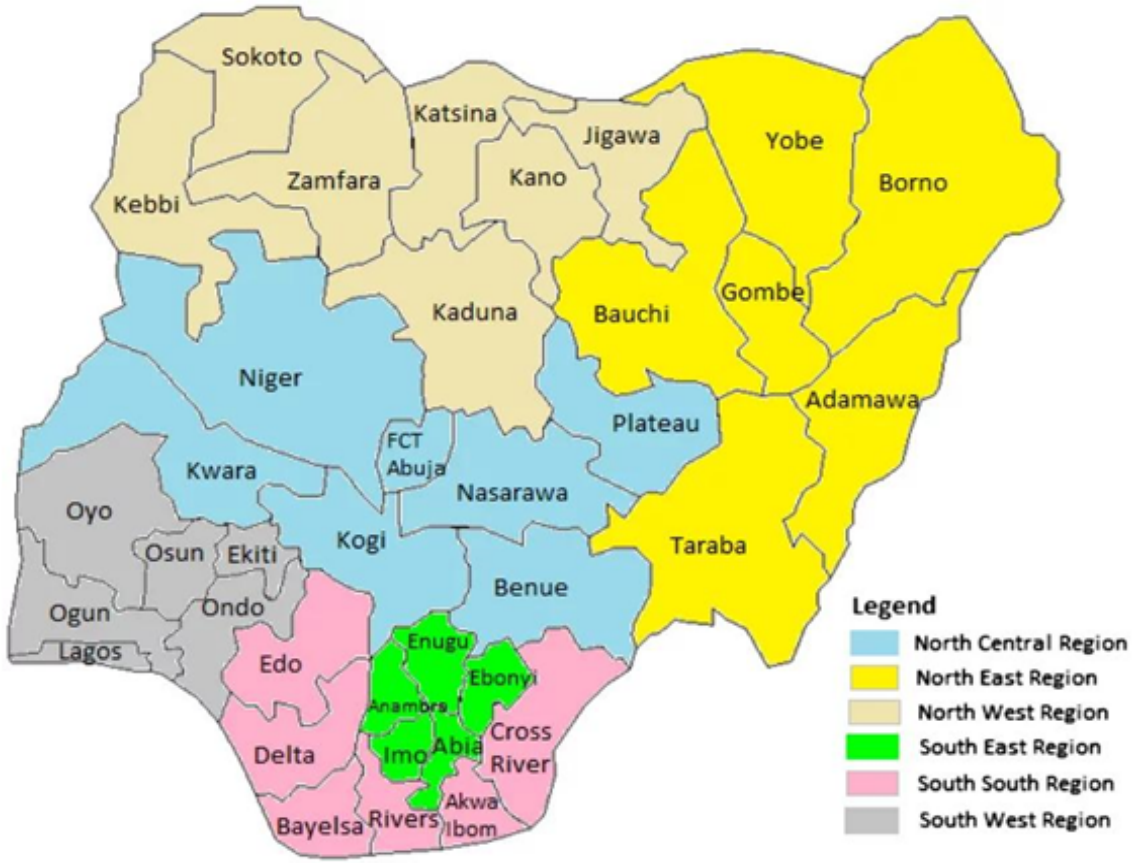

Figure 3 Map of Nigeria Showing the States, FCT and Six Geopolitical Zones.

11.30% was reported among HIV positive women and 16.70% of HIV positive pregnant women [46].

In North West Nigeria, 1.1% anti-*CMV* IgM was reported among pregnant women in ante-natal clinics in Birnin-Kebbi, Kebbi State while 93.30% with IgG antibodies in a related report [47;48]. An anti-CMV IgG of 97.80% was reported among pregnant women attending Usman Danfodiyo University Teaching Hospital (UDUTH) in Sokoto State [49]. Similarly, a prevalence of 4.82% IgG and 57.90 IgM *CMV* antibodies was reported among blood donors and 16.60% IgG with 7.10% IgM *CMV* antibodies among HIV positive patients in Sokoto [50; 51]. An anti-*CMV* IgG of 91.10% was reported among pregnant women attending Murtala Mohammed Specialist Hospital (MMSH), Kano, Nigeria[52]. Similarly, 100.00% prevalence of anti-*HCMV* IgG and PCR Viraemia of 14.40% in HIV infected adults with retinitis attending Aminu Kano Teaching Hospital (AKTH) was reported in Kano, Nigeria[53]. In Kaduna State, anti-*HCMV* IgG prevalence of 99.40% and IgM of 11.40% was reported among HIV patients (in Zaria, Kwoi, and Kaduna Metropolis) while a *CMV* IgG antibody prevalence of 94.80% was reported among pregnant women with 100% IgG antibody prevalence in non-pregnant women attending selected hospitals in Kaduna State [54; 55]. Similarly anti-*HCMV* IgM of 10.50% was reported among pregnant women attending ante-natal clinic at the General Hospital Kafanchan (GH Kaf), Kaduna State [56]. Furthermore. In Zaria Kaduna State, anti-*HCMV* IgG of 94.70% and IgM of 23.90% was reported among women of reproductive age in selected hospitals [57] (**Table 1**).

In the North Central/Middle Belt, a prevalence of 93.30% anti-*CMV* IgG seropositive and anti-*CMV* IgM of 3.50% with a significant association with gravidity has been reported among pregnant women in Makurdi, Benue State [58]. Similarly, anti-*CMV* IgM

Table 1. Cytomegalovirus in Northwest Nigeria.

S/N	State	Location	Test Type	IgG Prevalence Rate (%)	Active Infection/IgM Prevalence Rate (%)	Population
i.	Kebbi	Birnin Kebbi	ELISA	NRS	1.1	Pregnant Women-
		Birnin Kebbi	ELISA	93.3	NRS	Pregnant Women
ii.	Sokoto	UDUTH, Sokoto	ELISA	97.8	NRS	Pregnant Women
		Sokoto	ELISA	4.82	57.9	Blood Donors
		Sokoto	ELISA	16.6	7.1	HIV Patients
iii.	Zamfara	NRS	NRS	NRS	NRS	NRS
	Katsina, Jigawa					
iv.	Kano	MMSH Kano	ELISA	91.1	NRS	Pregnant Women
		AKTH Kano	ELISA/PCR	100	14.4	HIV Patients with Retinitis
			ELISA	98	NRS	Pregnant Women
v.	Kaduna	Zaria, Kwoi, Kaduna	ELISA	99.4	11.4	HIV Patients
		Kaduna	ELISA	94.8	NRS	Pregnant Women
		Kaduna	ELISA	100	NRS	Non -Pregnant Women
vi.		Kafanchan	ELIZA	NRS	10.5	Pregnant Women
vii.		Zaria	ELISA	94.7	23.9	Women of Reproductive Age

Keys=ELISA-Enzyme-Linked Immuno Sorbent Assay, NRS=No Report Seen, PCR=Polymerase Chain Reaction

Table 2. Cytomegalovirus in North Central and North East, Nigeria.

S/N	State	Location	Test Type	IgG Prevalence Rate (%)	Active Infection/IgM Prevalence Rate (%)	Population
i.	Benue	Makurdi	ELISA	93.3	3.5	Pregnant Women
ii.	Niger	Bida	ELISA	NRS	19.8	HIV Patients
		Minna	ELISA	96.2	2.6	Blood Donors
iii.	Kwara	Ilorin	NRS	98.2	24.9	Pregnant Women
iv.	Kogi	Lokoja	ELISA	NRS	21.7	Pregnant Women
v.	Nasarawa	Keffi	ELISA	74	NRS	Blood Donors
vi.	FCT	Abuja	ELISA	NRS	10.6	HIV Children and Adolescents
vii.	Plateau	Jos	ELISA	85.7	9.5	Recurrent Miscarriages Women
		Jos	ELISA	76.2	4.8	Normal Women
viii.	Gombe, Bauchi, Taraba and Adamawa	NRS	NRS	NRS	NRS	NRS
ix.	Borno	UMTH	ELISA	100	NRS	HIV Positive
		UMTH	ELISA	98.6	NRS	HIV Negative
x.	Yobe	Nguru	ELISA	90	NRS	Pregnant Women
		Nguru	ELISA	92.8	NRS	Women with Still Birth
		Nguru	ELISA	86.6	NRS	Miscarriage Women

Table 3. Genetic Variability, Effects of Human Cytomegalovirus in Northern Nigeria.

State	Location	Population	IgM Prevalence	Glycoprotein Gene	Variable Gene	Effect of Cytomelavirus
Kaduna	Kaduna	HIV Patients	11.4	gB	NRS	NRS
Niger	Bida	HIV Patients	19.8	gB	gB1, gB2	Deceases CD4 Counts
	Minna	Blood donors	2.6	NRS	NRS	Renders blood ineligible for donation
Kano	Kano	HIV Patients	14.4	NRS	NRS	Decreases CD4, Causes Retinitis
Plateau	Jos	Pregnant	9.5	NRS	NRS	Recurrent Miscarriages
Yobe	Nguru	Pregnant	NRS	NRS	NRS	Miscarriages in Women
		Women				
	Nguru	Pregnant Women	NRS	NRS	NRS	Still Birth

prevalence of 19.80% among HIV patients reported in Bida and 96.20% IgG with 2.60% IgM among blood donors in Minna, Nigeria State [59, 60]. In Kwara State, a *CMV* IgG prevalence of 98.20% and IgM of 24.90% was reported among pregnant women in Ilorin [61]. An anti-HCMV IgM prevalence rate of 21.70% was reported among pregnant women in Lokoja, Kogi State [62]. A prevalence of anti- *HCMV* IgG of 74.00% was reported among eligible blood donors in Keffi, Nasarawa State, while 10.60% anti-*HCMV* IgM among HIV infected Children and Adolescents in the Federal Capital Territory (FCT) Abuja, respectively [63, 64]. A Seroprevalence of *CMV* IgG of 85.70% and 9.50% IgM antibodies among women with recurrent miscarriages and 76.20% IgG and 4.80% IgM antibodies among normal women was reported in Jos Plateau State [65]. In the North East, no literature on the spread of Cytomegalovirus in Taraba, Gombe, Bauchi, and Adamawa States was available as at the time of this report, but 100.00% anti-CMV IgG was reported among HIV positive and 98.60% in HIV negative patients attending University of Maiduguri Teaching Hospital (UMTH) in Borno State [65]. Similarly, anti-*CMV* IgG prevalence of 90.00% was reported among pregnant women attending ante-natal in Nguru in Yobe State out of which 92.80% had still birth and 86.6% miscarriages (**Table 2**).

There was little literature on the molecular study of *Human Cytomegalovirus* in Northern Nigeria at the time of compiling this report. Nevertheless, *Cytomegalovirus* glycoprotein B gene (gB) detected through PCR was reported among anti-*CMV* IgM positive prevalence of 11.40 in HIV patients in Kaduna [54]. Similarly, Glycoprotein gB as well as variable genes gB1 (83.70%) and gB2 (16.30%), detected through PCR was reported among anti-*CMV* IgM positive HIV patients in Bida and 2.60% among blood donors in Minna all in Niger State. *Cytomegalovirus* decreases CD4 counts and contributes to retinitis among HIV patients, miscarriage in pregnant women and renders blood donors ineligible [53, 63, 65] (**Table 3**).

Conclusions and Recommendations

This review confirms previous reports that *cytomegalovirus* poses a significant threat to public health globally. The virus infects Immuno-compromised persons with complications development. The presence of immunoglobulin g (IgG) signifies previous infection while IgM is an active infection. Active infections with *Cytomegalovirus* have been reported among pregnant women in Kebbi State (IgM 1.10%), IgM of 57.90% among blood donors, and 7.10% in HIV patients in Sokoto State, 14.40% IgM among HIV patients with retinitis in Kano, and 11.40%, among HIV patients, 10.50% in Pregnant women and 23.90% among women of reproductive age respectively, in Kaduna State all in Northwest Nigeria. Similarly, in the North Central, active infections were reported in Benue (3.50%) among pregnant women, 19.80 among HIV patients in Bida, and 2.60% among blood donors in Niger State, 24.90% among pregnant women in Kwara State, 21.70% among pregnant women in Kogi State, 10.60% in HIV Children and adolescent in the FCT Abuja, 9.50% among recurrent miscarriage women as well as 4.80% in normal women in Plateau State respectively .There is no report of active infections in the whole of the North Eastern States Such as Gombe, Bauchi, Adamawa and Taraba States respectively but passed infections with IgG reports in Borno State (100% and 98%) and Yobe State (90%, 92.80% and 86.60%) respectively. Therefore, *cytomegalovirus* has been reported in Northern Nigeria among HIV patients, pregnant women, and blood donors at different locations within the region. The virus has been associated with decreased CD4 count among HIV patients, recurrent miscarriages, and still births among pregnant women, renders blood ineligible for donation, and is implicated in retinitis among HIV patients. Therefore, regular medical checkups, avoidance of exposure of soft tissues and open sores to infected body fluids, and medical attention to infected cases to avoid complications and viral spread are recommended for proper control of the virus. More study is recommended in Gombe, Adamawa, Bauchi and Taraba States respectively. Adequate viral control is necessary for the improvement of public health.

Conflict of Interest

All authors declare no conflict of interest, financial or non-financial.

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