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Human Cytomegalovirus infection in Pregnancy- a neglected public health problem.Abdullahi Sani Gadama¹.Hospital Management Board, P.M.B: 0054, Bauchi State, Nigeria¹.**Author for Correspondence:** drabdullahigadama@gmail.com / +234-803-796-9591**Summary**

Human Cytomegalovirus (HCMV) is one of the most successful human parasites. It survives comfortably in its human host in latent form and could be reactivated under favoring circumstances. It is transmitted both vertically from mother to foetus and horizontally from one person to another. It is the most common congenital cause of mental retardation and auditory disorders in children. Infection with HCMV in immunocompetent individual is usually beneath the threshold of clinical recognition but it can cause serious disease in developing foetus and immunocompromised. HCMV infection has worldwide endemic distribution with no seasonal variation. Prevalence is higher in communities with low socioeconomic status and low level of personal hygiene. Infection with HCMV present in virtually every population that has been tested with prevalence among women of reproductive age ranging from 45% in developed countries to 100% in developing nations. Evidence has shown that HCMV Primary infection in pregnant women of developed nations is associated with high risk of transmission to the developing foetus. With the high prevalence of HCMV in sub-Saharan Africa, it is possible for non-primary HCMV infection to account for the main burden of Congenital HCMV infection in these areas. The risk of transmission to the developing foetus is even higher in pregnant women with HCMV/HIV co-infection. Awareness and knowledge of HCMV is often hidden in a lacuna, as a result, no intervention policy for the prevention and control of HCMV across nations worldwide. It is important therefore, to initiate a worldwide awareness campaign on HCMV infection and its consequences for the purpose of prevention and control since there is yet to be

consensus by the scientific societies on the treatment options.

Keywords: Cytomegalovirus, pregnant women, pathogenesis, immune response, prevalence, therapeutics, prevention, Awareness.

Introduction

Human Cytomegalovirus (HCMV) belongs to the *Betaherpesvirinae* subfamily of *Herpesviridae*. Herpesviridae family members include; Herpes Simplex virus (HSV) type 1 and 2, Varicella Zoster virus (VZV) and Epstein-Barr virus (EBV). HCMV is ubiquitous and morphologically indistinguishable from other human herpesviruses (Sinzger *et al.*, 1995). It shares many attributes with other herpesviruses which includes; the envelope (a lipid bilayer membrane with several glycoproteins), tegument (structure between envelope and capsid, consisting of more than 25 proteins), icosahedral capsid, and a core that contains the linear double – strand DNA genome (Yu *et al.*, 2003).

HCMV possesses the largest genome of the herpesviruses (~240 kilobase pairs). Its replication is slow, similar to that obtained for HSV with the sequential appearance of immediate early, early, and late gene products. Strains of HCMV demonstrate considerable genomic and phenotypic heterogeneity, and restriction endonuclease analysis of viral DNA has been useful for distinguishing strains epidemiologically. Variations in antigenicity have also been observed but thought to be of no clinical significance (Walter *et al.*, 2001).

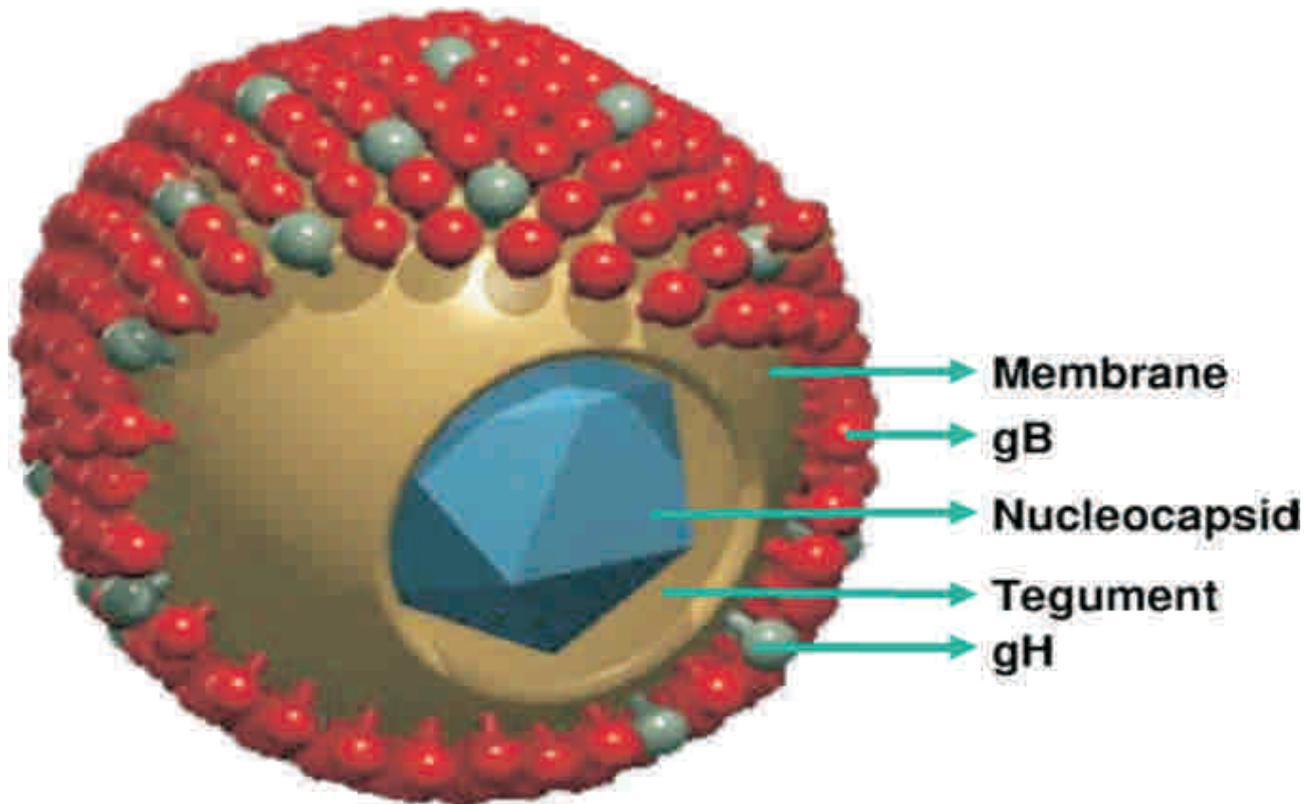


Figure 1. Virtual three-dimensional model of HCMV showing various components of the virus. (Adapted from Crough and Khanna, 2009/ <http://www.biografix.de>).

HCMV consists of a double-stranded linear DNA core enclosed within an icosahedral nucleocapsid that is collectively enveloped by the tegument which is the proteinaceous matrix of the virion (Crough and Khanna, 2009; Chen *et al.*, 1999). The tegument is equally covered by a lipid bilayer that contains a number of viral glycoproteins. A mature HCMV has a diameter ranging from 200 to 300 nanometers (Crough and Khanna, 2009; Knipe, *et al.*, 2007). Within the tegument, are contained the predominant amount of the virion proteins especially the lower matrix phosphoprotein 65 (pp65), referred to as the unique long 83 (UL83). Other important HCMV tegument proteins include the virion trans-activator pp71 (upper matrix protein, UL82 gene product), the herpesvirus core virion maturation protein pp150 (large matrix phosphoprotein, UL32 gene product), the largest tegument protein (UL48 gene product), and the UL99-encoded pp28 (Crough and Khanna, 2009; Varnum *et al.*, 2004). Other tegument proteins also exist, though in a small quantity together with some cellular and viral RNA particles (Crough and Khanna, 2009; Knipe *et al.*, 2007).

Important functions of the tegument can basically be

summarized into two categories. Those that play a structural role and are important for the assembly of virions as well as the disassembly during entry, and those that modulate the host cell response to infection (Crough and Khanna, 2009; Knipe *et al.*, 2007). The host cell endoplasmic reticulum-Golgi intermediate compartment-derived lipid bilayer envelope that is surrounding the tegument, contains at least 20 virus-encoded glycoproteins (glycoprotein B (gB), gH, gL, gM, gN, and gO) with varied functions (Crough and Khanna, 2009; Knipe, *et al.*, 2007).

Life cycle of a Human Cytomegalovirus

HCMV enters human cells either through direct fusion or through the endocytic pathway (figure 2). The virus attaches to the cell via interactions between viral glycoproteins (e.g., gB and gH) and a specific surface receptor(s) (platelet-derived growth factor α), followed by the fusion of the envelope with the cellular membrane to release nucleocapsids into the cytoplasm. These nucleocapsids are translocated into the nucleus, where viral DNA is released with subsequent initiation of IE-1/IE-2 genes expression (Crough and Khanna, 2009). Viral replication and maturation follow the stimulation and parallel

accumulation of viral synthesis function. This process involves the encapsulation of replicated viral DNA as capsids, which are then transported from the nucleus to the cytoplasm. Secondary envelopment occurs in the cytoplasm at the endoplasmic reticulum

(ER)-Golgi intermediate compartment. And finally a complex two-stage final envelopment and egress process that leads to virion release by exocytosis at the plasma membrane occurs (Crough and Khanna, 2009).

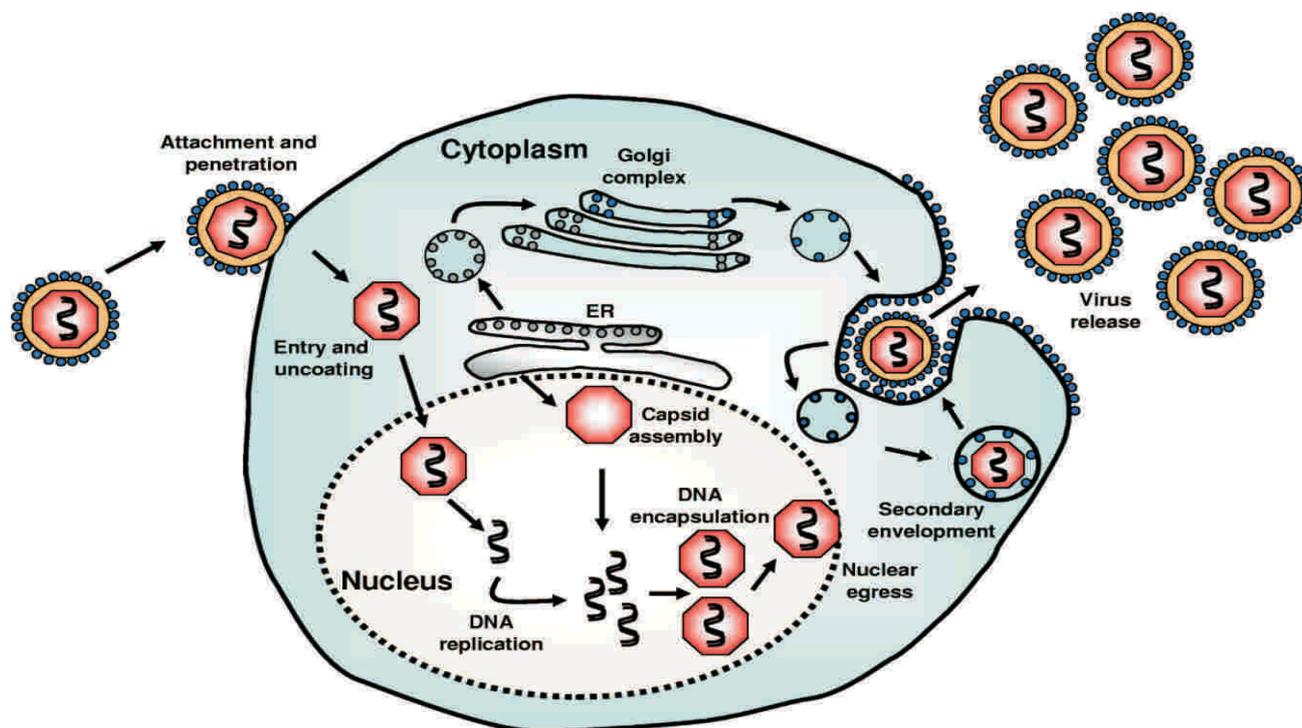


Figure 2. Life cycle of HCMV in a human cell (Adopted from Crough and Khanna, 2009)

Forms of Human Cytomegalovirus Infection

Infection with HCMV could take either primary or non-primary forms. HCMV infection in a previously seronegative person (achieved via enzyme-linked immunosorbent assay) is termed primary form of infection. Primary infection is characterized by a period of active virus replication with virus shedding in saliva, urine, milk, and genital secretions. It is referred to as the viremic phase and in some cases, an infectious mononucleosis syndrome may be the presentation (Revello *et al.*, 1998).

Reactivation can occur in previously infected person following virus dormancy usually in immunosuppressive conditions. With the knowledge of the emergence of several strains of HCMV through molecular studies, reinfection can therefore occur even in immunocompetent individuals when the subject is re-infected by a virus distinct from the initial one (Yinon *et al.*, 2010). Recurrent infection arises following reactivation of previous infection and/or re-infection by a virus distinct from the initial one. (Yinon *et al.*, 2010; Alford *et al.*, 1990).

Non-primary infection with HCMV includes recurrent infection, reinfection and reactivation of primary infection. Reinfection and reactivation constitute a sub-set of non-primary infection called the Secondary HCMV infection (Revello *et al.*, 2011).

Mode of Human Cytomegalovirus Acquisition.

HCMV can be acquired horizontally or via vertical route. HCMV is spread horizontally through close personal contact with people who excrete the virus in body fluids (e.g. saliva, urine, cervico-vaginal secretions and semen), through organ transplantation or via blood transfusion (Yeroh *et al.*, 2015; Pass, 2001).

Transmission of infection has been shown to occur from asymptomatic excretors to other children and, in turn, to seronegative parents in a study conducted in day care centers. Infected adults also excrete virus for prolonged periods after primary infection or reactivation of latent infection especially the immunocompromised. Latent infection, which may reside in leukocytes and their precursors, can be

transmitted by transfusion and organ transplantation (Walter *et al.*, 2001).

Transmission of HCMV can be from mother in-utero (vertically) through placenta from blood spread to the foetus during maternal viremia, or at birth through exposure to infected cervical and vaginal secretions and postnatal by ingestion of HCMV-positive saliva via kissing or breast milk (Hyde, 2014; Kenneson and Cannon, 2007; Pass *et al.*, 2006).

Pathogenesis of Human Cytomegalovirus infection and host immune response.

Both the innate and acquired wings of immunity play synergistic viral roles in the host immunity against HCMV infection (Gadama *et al.*, 2017). Primary infection with HCMV in healthy individuals typically begins with the entry and replication of the virus in the mucosal epithelium of the upper alimentary, respiratory, or genitourinary tracts as illustrated in figure 3 below (A). The virus then disseminates to monocytic cells of myeloid lineage including monocytes and CD34⁺ cells, where it establishes latent infection (B). Restricted viral gene expression is observed in these latently infected cells, thus limiting their immune recognition by effector

cells (Crough and Khanna, 2009). The differentiation of these virus-infected monocytes into macrophages can initiate productive infection (C). Virus particles or virus-associated dense bodies can be processed by professional antigen-presenting cells (e.g., Dendritic Cells), which can stimulate antigen-specific T cells (D). In addition, these Dendritic Cells activated through Toll Like Receptors can also secrete a range of cytokines/chemokines, which activate the innate arm of the immune system (e.g., NK cells) (D). Virus-infected macrophages can also directly stimulate antigen-specific T cells (C). These activated T cells (CD8⁺, CD4⁺, and/or γ^{δ} T cells) and NK cells can directly lyse virus-infected cells by cytolysis or block virus replication through the secretion of cytokines such as IFN- γ and/or TNF (E) (Crough and Khanna, 2009).

Another important arm of adaptive immunity involves B cells, which are also activated by the professional antigen-presenting cells and control extracellular virus through antibody-mediated neutralization (F). The antibodies produced by the B cells limits penetration of HCMV by binding to the gB receptors and hence, rendering the virus useless (Crough and Khanna, 2009).

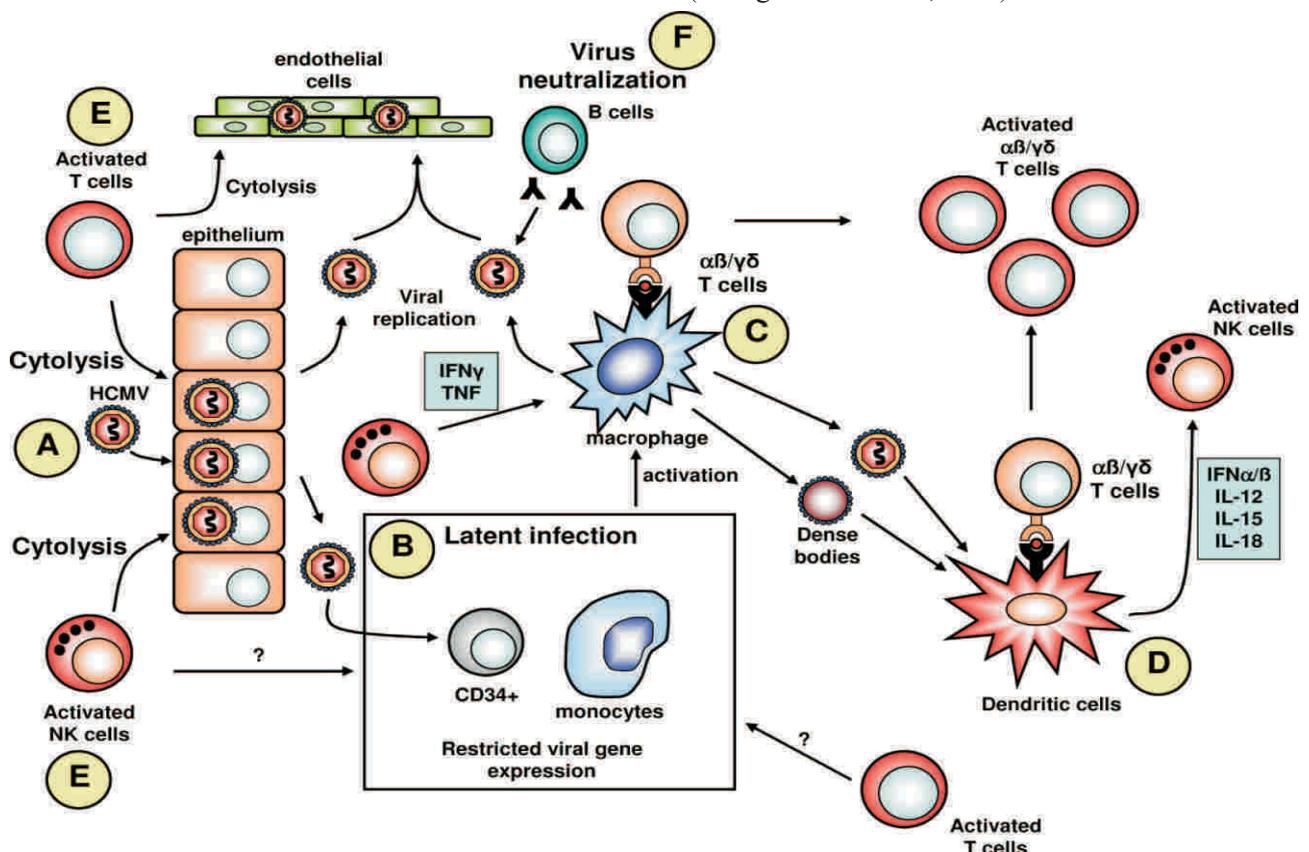


Figure 3. Immune control of HCMV by innate and adaptive immunity (Adopted from Crough and Khanna, 2009).

The mechanisms and sites of HCMV latency are not completely understood. However, leukocytes, especially mononuclear leukocytes, are suspected to contain latent virus. Organs such as the kidneys and heart were also said to harbor the virus, but the exact cells still remain unknown (Walter *et al.*, 2001). In vitro, HCMV DNA can be demonstrated in monocytes showing no cytopathology, indicating a restricted growth potential and hence latency (Walter *et al.*, 2001). Latent HCMV could be reactivated giving rise to reactivation form of HCMV infection, especially in immunosuppressive conditions like HIV/AIDS.

HCMV is capable of infecting most of the body cells, acting in the cytoplasm and the nucleus of the infected cells, forming inclusions bodies (Naddeo *et al.*, 2015; Schleiss, 2011). Histologically, nuclear inclusions are seen in the infected cells giving it an “owl eye cells” appearance. Additionally, HCMV produces perinuclear cytoplasmic inclusions and enlargement of the cell termed “cytomegaly”, a property which gives the virus its name (Walter *et al.*, 2001).

Cellular damage appears to be caused directly by the viral lytic activities or indirectly by the immune response of the host (Walter *et al.*, 2001). An example of cellular damage resulting from a direct cytopathic effect is retinitis seen in advanced AIDS patients, in which blindness occurs as a result of a necrotizing infection caused by the virus. HCMV pneumonitis frequently manifests in organ transplant recipients with life-threatening clinical symptoms and often subtle pathological changes histologically. Extensive inflammation occurs which is usually accompanied by mild viral replication, suggesting immune-mediated activities as the primary pathologic mechanism in HCMV pneumonitis (Walter *et al.*, 2001).

Human Cytomegalovirus infection in Pregnancy.

HCMV infection is usually an asymptomatic infection in immunocompetent individuals, symptomatic disease is often non-specific and manifest as infectious mononucleosis which is characterized by malaise, headache, sore throat and fatigue. Fever commonly occurs and could persist for weeks in 98% of cases following infection. Lymphadenopathy, pharyngitis and splenomegaly are each seen in 30% of HCMV patients (Yeroh *et al.*, 2015; Pass, 2001).

In pregnant immunocompetent women, seroconversion usually occurs in 1% to 4% of all pregnancies and is usually higher in women with low socioeconomic status and poor personal hygiene (Yinon *et al.*, 2010; Hagay *et al.*, 1996; Hanshaw, 1995).

HCMV infection is dependent on multiple factors, including socioeconomic status, age and occupation (Betts, 1983). Seropositivity correlates with increasing parity, lower socio-economic level, older age, number of sex partners and immune status such as HIV, cancer chemotherapy, organ transplantation etc. (Chandle *et al.*, 1985).

In a study conducted in United State of America to determine the seroprevalence of HCMV, Age was found to be statistically significant to HCMV prevalence (Bate, *et al.*, 2010). In Sudan, seroprevalence was reported to be associated with history of miscarriage (khairi, *et al.*, 2013).

A study conducted in Kafanchan Nigeria, revealed seroprevalence of HCMV to be associated with increasing age (Deborah *et al.*, 2015). In a recent study conducted in North-western Nigeria, HCMV infection in pregnancy was associated with polygamy practice (Gadama *et al.*, 2018). This finding is not surprising since the region is one of the areas in Nigeria with a high rate of polygamy practice (Gadama *et al.*, 2018; Verma and Sangha, 1982).

Prevalence of Human Cytomegalovirus infection in healthy pregnant women.

HCMV infection has worldwide endemic distribution with no seasonal variation (Revello *et al.*, 2011). Although HCMV is widely distributed, its epidemiology is diverse as its transmission is deeply related to low sanitary conditions, high population density and immune status of the host. Serological surveys have shown HCMV infections virtually present in every population that have been tested (Okwori, *et al.*, 2008) with seroprevalence among women in the reproductive age ranging from 45% in developed countries to 100% in developing countries (Plosa *et al.*, 2012).

Reports have shown that the African continent has the highest prevalence of CMV IgG antibodies (Cannon *et al.*, 2010). Seroprevalence of 72.2% and 96.0% have been reported in Western Sudan and Egypt (Hamdan *et al.*, 2011). Equally in

Omdurman maternity Hospital of Sudan, Seroprevalence was reported to be 97.5% and 6% for IgG and IgM respectively (Khairi *et al.*, 2013).

Situation is similar in other developing nations across continents. In Asian countries such as Malaysia, the seroprevalence of HCMV IgG antibodies among pregnant women was as high as 84.0% (Saraswathy *et al.*, 2001). Similarly, a study conducted in Khorramabad of Iran, reported a seroprevalence of 90.4% (Delfan-Beiranvand, 2011). In another study conducted in Israel to determine seroprevalence of HCMV in parturient Israeli population, 84.3% prevalence was reported (Stein, *et al.*, 1997). In China and Korea as well, prevalence was equally high with seroprevalence of 95.6% (Meng *et al.*, 2011) and 98.1% (Seo *et al.*, 2009) respectively.

In Yemen, Iraq and Palestine also, prevalence reported was very high with values of 98.7% (Alghalibi *et al.*, 2016), 100% (Al-Jurani *et al.*, 2014) and 99% (Neirukh *et al.*, 2013) respectively.

Seroprevalence of HCMV is completely different in the developed world where seroprevalence was significantly lower. This is expected due to high level of personal and environmental hygiene coupled with the fact that most people are relatively enlightened to practice personal preventive measures.

A serological survey conducted in London found 54.4% of the study women were seropositive for HCMV (Yeroh *et al.*, 2015; Tookey *et al.*, 1992). In France the seroprevalence obtained was 46.8% (Picone *et al.*, 2009) which is similar to those obtained for Finland and United States of America with 56.3% (Alanen *et al.*, 2005) and 60.0% (Staras *et al.*, 2006) seroprevalence respectively.

In Nigeria, the prevalence of HCMV infection is grossly alarming across all geographical locations. A case was reported in 2004, of three siblings from a monogamous family in Osun State, Nigeria who presented with a history of visual impairment/blindness due to HCMV infection (Bernice, 2008).

In Lagos South-Western Nigeria, 97.2% Seroprevalence was obtained (Akinbami *et al.*, 2011). Similarly, high seroprevalence of 96% was obtained in another study conducted in Southern

Nigeria (Ogbaini-Emovoni *et al.*, 2013).

In North-Central Nigeria, serological survey conducted in Bida of Niger State revealed seroprevalence as high as 84.2% (Okwori *et al.*, 2008). The situation is similar in North-western Nigeria where Seroprevalence of 98.7% (Ahmad *et al.*, 2011), 94.8% (Yeroh *et al.*, 2015), 87.4% (Gadama *et al.*, 2018) was found for Sokoto, Kaduna and Jigawa States respectively. In Maiduguri of North-Eastern Nigeria, 79.1% prevalence was obtained for IgG antibody (Babayo *et al.*, 2014). These results show that HCMV is on the rise in Nigeria.

Congenital Human Cytomegalovirus infection.

Several studies have demonstrated a strong association between primary HCMV infection of the mother and vertical HCMV transmission. The risk of congenital infection is approximately 40% in babies born to mothers who acquire a primary HCMV infection after conception. In contrast, the risk is only about 1% in infants born to mothers with non-primary HCMV infection (Dollard *et al.*, 2014). Since the main burden of congenital infections in developed nations results from primary infections, non-primary infections may therefore, represent the main cause of HCMV vertical transmission in developing countries since higher seroprevalence was documented in these areas (Saldan *et al.*, 2017; Mussi-Pinhata *et al.*, 2009).

Congenital infection could also result from reactivation of HCMV infection in the mother, with subsequent spread to the foetus. Though, such infection rarely leads to congenital abnormalities due to protection developed in the foetus via passively transferred maternal antibody (Walter *et al.*, 2001).

Congenital HCMV infection is estimated to affect 0.2–3% of live births in Western Europe and up to 14% in developing countries (Mwaanza *et al.*, 2014). Congenital HCMV infection occurs in approximately 40,000 newborns each year in the United States (Coll, 2009).

About 5-10% of newborns with congenital HCMV infection show clinical manifestations including petechiae, jaundice, hepatosplenomegaly, and microcephaly at birth. In addition, studies have demonstrated that a proportion of asymptomatic

newborns with evidence of congenital infection face a significant risk of late-onset sequelae, such as sensorineural hearing loss (SNHL) and neurological behavioral problems, including mental retardation, cerebral palsy, and developmental disabilities (Pass, 2001). It has been estimated that about 60%–90% of children with symptomatic and 10%–15% asymptomatic Congenital HCMV infection in the neonatal period will develop long-term neurological damage when followed up at birth (Griffiths and McLaughlin, 2004).

In absolute terms, Congenital HCMV infection occurs in 30,000 to 40,000 newborns each year in United States. Approximately 9,000 of these children have developed permanent neurological sequelae. The death rate of symptomatic congenital HCMV infection is estimated to be about 30% (Neto *et al.*, 2004).

About two thirds of infants in African studies show serological evidence of infection by 3 months of age and 85% are infected by a year (Gumbo *et al.*, 2014). By adolescence, HCMV IgG is thought to be virtually universal in sub-Saharan African populations (Chakraborty *et al.*, 2003).

The prevalence of congenital HCMV in different African populations is likely to vary; data are sparse but studies range from rates of 2.9% in South Africa (Manicklal *et al.*, 2014), to 3.8% in Zambia (Mwaanza *et al.*, 2014), 5.4% in the Gambia (Van der Sandel *et al.*, 2007). A study conducted in Lagos South-western Nigeria revealed a prevalence of 3.8% (Olusanya *et al.*, 2015). These results show the endemic nature of HCMV infection in the world.

HCMV/HIV Co-infection in Pregnancy.

Although HCMV infections are beneath the threshold of clinical recognition, they can cause serious diseases in foetuses and in immunocompromised individuals (Dollard *et al.*, 2014). Human immunodeficiency virus (HIV) attacks the cells of the immune system, exposing the patient to a myriad of opportunistic infections. People living with HIV have compromised immune systems and are at a much greater risk for serious repercussions from common illnesses and opportunistic infections (OIs) caused by viruses, bacteria, fungi and parasites (Akinwale *et al.*, 2013).

HCMV is a major opportunistic pathogen in patients with HIV infection. In the absence of highly active antiretroviral therapy (HAART), patients with CD4 counts less than 50–100 cells/mm³ are at risk of HCMV infection and its consequences. Retinitis, enterocolitis, esophagitis, gastritis, immune recovery vitritis -posterior segment inflammation and pneumonitis are some of the presentations (Salmon-Ceron *et al.*, 2000).

A complex interaction exists between HIV and HCMV, including mode of pathogenesis and shared mode of in utero, perinatal, and post-natal routes of transmission (Guibert *et al.*, 2009). In the Western world, the rate of HCMV seropositivity is much higher among adults with risk factors for acquisition of HIV infection (Gianella *et al.*, 2015). This observation suggests a shared risk factors for acquisition of the two viruses as well as raising the possibility that HIV infection may be a direct risk factor for HCMV acquisition in adults. The reciprocal scenario may also apply, as data from Africa suggest that HCMV infection may be a risk factor for HIV transmission; a study in KwaZulu-Natal (South Africa) found an independent association between HCMV in breast milk and postnatal mother-to-child transmission of HIV (Viljoen, *et al.*, 2015).

HCMV infection is particularly an important problem among HIV-infected pregnant women (Kovalleva, *et al.*, 2009). Co-infection with HCMV in HIV-positive pregnant women is associated with perinatal mother-to-child transmission (MTCT) of both viruses (Reitter *et al.*, 2016). HCMV is one of the viruses most frequently transmitted to developing fetus, causing birth defects in new born and immune defect in later life with subsequent increase in morbidity and mortality (Stern and Tucker, 1978).

Several mechanisms may explain the increased prevalence of HCMV in HIV-infected neonates; first, HIV-infected mothers who transmitted HIV in utero would be expected to be more immunosuppressed and therefore at increased risk of reactivating and transmitting HCMV. Secondly, immunosuppression associated with foetal HIV infection may result in higher risk of HCMV acquisition in utero. Alternatively, foetal HCMV co-infection may facilitate HIV acquisition in utero (Slyker *et al.*, 2009).

In resource challenging settings, a large proportion of children undergo simultaneous primary HIV and HCMV infection (Slyker *et al.*, 2009). Thus, among HIV-positive children in Africa, the majority are co-infected with HCMV by their first birthday (Gumbo *et al.*, 2014), and almost all are co-infected by the time they reach their teens (Chakraborty *et al.*, 2003). The growing epidemic of co-infected adolescents may have significant clinical impact in these populations. In comparison, a study from North America reports a lower rate of early co-infections, finding that 40–50% of HIV/HCMV co-infected children had acquired HCMV before their first birthday (Kovacs *et al.*, 1999). Despite these data among the HIV/AIDS infected population, no evidence of intervention programme on HCMV/HIV co-infection that has yet been incorporated into HIV/AIDS patient's management in most countries worldwide.

Prenatal diagnosis of Human Cytomegalovirus infection

The first step in the prenatal diagnosis of congenital HCMV infection is determination of maternal primary and secondary infection by serological testing (Lazzarotto *et al.*, 2000). It is important to note that virus detection alone in the amniotic fluid does not determine whether the foetus is going to show signs of infection. Following up with ultrasounds is important to observe if there are any central nervous system abnormalities. After delivery, otologist evaluation is necessary to investigate hearing impairment, which is the most common sequelae of HCMV infection (Lazzarotto *et al.*, 2000).

The gold standard method for HCMV foetal infection diagnosis is the detection of viral DNA by polymerase chain reaction (PCR) of the amniotic fluid. However, amniocentesis is an invasive procedure and can only be performed after 18 weeks of gestation and (Boppana *et al.*, 1992) weeks after seroconversion (time it takes the foetus to excrete the virus through the urine) (Benoist *et al.*, 2013)

Therefore, in women with proven HCMV infection, the second step is to identify fetal infection by non-invasive (ultrasound examination) and invasive (amniocentesis) prenatal tests (Lazzarotto *et al.*, 2000) as summarized in the figure 4 below.

In pregnant women, the goal standard for the diagnosis of primary HCMV infection is ascertained when seroconversion is documented, i.e., the de novo appearance of virus-specific IgG in the serum of a pregnant woman who was previously seronegative. However, such an approach is feasible only when a screening program is adopted and seronegative women are identified and monitored prospectively (Revello and Gerna, 2002). Seroconversion occurs in 1% to 4% of all pregnancies and is higher in women of low socioeconomic status or who have poor personal hygiene (Yinon *et al.*, 2010; Hagay *et al.*, 1996; Hanshaw, 1995).

Since pre-conception serologic screening for HCMV is not routinely performed in most countries including Nigeria, seroconversion data may often not be available. As such the detections of HCMV IgM and low-avidity IgG remains the only option for primary HCMV infection detection as it has been proven to be effective (Saldan *et al.*, 2017; Daiminger *et al.*, 2005). However, IgM can also be detected in 10% of recurrent infections and can also be detected for significant months following primary infection (Yinon *et al.*, 2010; Griffiths *et al.*, 1982). Therefore, the group of women designated HCMV-IgM positive could include women with primary infection acquired before pregnancy and a few women with recurrent infections (Yinon *et al.*, 2010; Drew, 1988).

In circumstances with an uncertain diagnosis, it is recommended to perform an antigen avidity assay. Antigen avidity test successfully distinguish primary from non-primary HCMV infections. Avidity is defined as the aggregate strength with which a mixture of polyclonal IgG molecules binds to multiple antigenic epitopes of proteins (Hazell, 2007). Over months, IgG gradually matures reflective of antigen-driven selection of B cells producing IgG of increasing affinity (Hyde, 2014). IgG antibodies produced during the first few months following primary infection exhibit low avidity (i.e., they bind weakly to the antigen), whereas antibodies produced by 6 months post-infection exhibit high avidity (Revello and Gerna, 2002).

Therapeutics

The treatment of HCMV infections is complex and yet controversial. There is currently no FDA-approved treatment for congenital HCMV infection (Sara *et al.*, 2016). Even if an approved

treatment or a vaccine can be developed and becomes widely available, the best alternative for reducing the incidence of congenital HCMV at the present time appears to be more widespread use of basic hygiene practices among pregnant women to avoid transmission via saliva or urine from young children (Pass and Anderson, 2014; Adler and Nigro, 2013; Swanson and Schleiss, 2013).

Antiviral drugs like ganciclovir, cidofovir and foscarnet were reportedly being used in immunocompromised individuals. However, their marked renal toxicity, haematological toxicity and teratogenic effects restrict their use in pregnancy (Benoist *et al.*, 2013).

Oral valganciclovir was used in cases of congenital infection. The drug was able to reach therapeutic levels in both maternal and foetal blood and also had effect on the viral load in fetal blood (Gadama *et al.*, 2018; Naddeo *et al.*, 2015; Jacquemard *et al.*, 2007). Study on the use of Valganciclovir to treat symptomatic congenital HCMV infections indicates promising results (Kimberlin *et al.*, 2015).

Immunotherapy has also been employed. HCMV hyper-immune globulin was used for maternal primary CMV infection showing encouraging results for prevention and treatment of congenital infection with no signs of side effects (Benoist *et al.*, 2013). The study has also shown that hyper-immune globulin has immunomodulatory effects that can decrease the pathogenic effects of HCMV (Gadama *et al.*, 2018; Naddeo *et al.*, 2015; Nigro *et al.*, 2015).

Control of Cytomegalovirus infection.

Until a potent vaccine against HCMV is produced, the ultimate option is personal preventive measures including hand washing after change of diapers and handing secretion from babies. Reports have shown that while the HCMV virus can live for up to 15 minutes and 5 minutes on hard plastic objects and on crackers respectively, no viable virus was recovered after washing hands with soap, sanitizer, or even just with water (Stowell *et al.*, 2014).

The Centers for Disease Control and Prevention (CDC) recommends regular hand washing, particularly after changing diapers as an effective way of reducing the exposure as well as incidence

of HCMV infection (Sara *et al.*, 2016; CDC, 2008). Studies have demonstrated that hand washing and other preventative steps are effective. For instance, a study has found that only 3% (one of 37) of HCMV seronegative pregnant women with an infected young child who were educated about using simple hygiene practices in their daily routines seroconverted to HCMV during pregnancy, while 42% (65 of 154 women) of pregnant women who were not educated seroconverted (Sara *et al.*, 2016; Adler and Nigro, 2013).

Awareness of Human Cytomegalovirus infection.

It is evident that many children present with several neurological diseases to the pediatrics neurology clinics (Wammanda *et al.*, 2007). However inadequate knowledge and facilities for laboratory diagnosis of such conditions often make the likely etiologies remaining unknown. There are several reports of neurological sequelae in children that are traced to maternal HCMV infections (Dollard *et al.*, 2014). The worldwide neglect of this problem is underscored by the continued lack of awareness of congenital HCMV among health care workers and the general public (Mussi-Pinhata *et al.*, 2009). HCMV infection is therefore said to be a neglected public health issue.

The first step in improving hygiene practices that will likely lead to reduction in the prevalence of HCMV infection is ensuring that the health personnel and the general public (especially men and women of childbearing age) knows about the existence and consequences of HCMV. Assessing the knowledge of health personnel is paramount to the creation of awareness campaign for HCMV infection, since they form the bed-rock for information dissemination to their clients.

In Nigeria as well as most developing countries, there seem to be paucity of data regarding the awareness of HCMV infection despite the rising prevalence. Studies were conducted in some parts of the world on the knowledge of health personnel as well as pregnant women about HCMV infection. In Netherland for instance, a study was conducted to determine the knowledge of HCMV infection among doctors. The knowledge of doctors was reported to contain significant gaps as most doctors in Obstetrics and Gynecology were not aware of the precise transmission routes of HCMV and more

than one-third of the respondents assumed that treatment of HCMV was available (Korver *et al.*, 2009).

In Geneva, Switzerland as well, a study was undertaken to assess the level of awareness regarding HCMV infection and its consequences among women delivering at University of Geneva Hospital. Only 39% of the respondents were aware of HCMV infection, and only 19.7% had received information about preventive measure (William *et al.*, 2015). The result could be worst in developing countries considering their literacy level.

There have been a number of public health efforts to increase awareness about HCMV infection. In 2013, the Utah Legislature unanimously passed the first HCMV public health initiative law (Sara *et al.*, 2016; McVicar, 2014). The law is the first of its kind and made it mandatory that the Utah Department of Health to implement a public health education campaign to inform women who are pregnant or might become pregnant about HCMV infection, its consequences as well as preventive measures. The law also mandates an education campaign for medical and child-care professionals. Early Hearing Detection and Intervention (EHDI) program within the State's Department of Health was charge

d with the implementation process (Sara *et al.*, 2016).

A number of non-profit organizations are also working to raise awareness of HCMV infection. The National HCMV Foundation in 2015 was founded when four non-profit HCMV organizations joined forces with an aim to “empower women, parents, families, and local community networks through grassroots engagement to facilitate conversations about HCMV and to champion the cause against congenital HCMV (Sara *et al.*, 2016).

The Nigerian maternal health policy provides for the screening of malaria, HIV and syphilis during antenatal care, consistent with the recommendations of the World Health Organization (WHO, 2012). However, the policy does not provide for the screening of HCMV in pregnant women. There is no evidence of capacity for CMV detection at all levels of health facility laboratories in Nigeria.

Conclusion

HCMV can best be described as a Cinderella, since emphasis is yet to be made on awareness, diagnosis and treatment especially in Sub-Saharan Africa where the prevalence is relatively higher. There is evidence of neurological sequelae in children that are traced to maternal HCMV infection. Despite these evidences, no intervention policies nor capacity for diagnosis of HCMV infection in most nations across the world. This is compounded by the poor level of awareness by both health personnel and the general population on the consequence of HCMV infection on the developing foetus and the immunocompromised. Hence, HCMV infection is said to be a neglected public health problem.

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