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Editorial

Congenital cytomegalovirus infections in sub-Saharan Africa – a neglected and growing problem

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Cytomegalovirus (CMV) infection is ubiquitous and is one of the most common viral infections of humans. It belongs to the 'herpes' family of viruses and encodes over 160 proteins, many of which have immunomodulatory functions. CMV infection can be acquired at any age, and most initial infections go unnoticed, although some individuals develop 'glandular fever'-like symptoms, which usually resolve (Mocarski *et al.* 2007). Like all herpesvirus infections, once a person acquires primary infection, CMV remains in a latent viable form within the body from which it may periodically reactivate under circumstances of immunosuppression. CMV causes two well-established serious clinical problems that are of major public health importance worldwide: (i) congenital CMV infections due to primary maternal CMV infection subsequently transmitted *in utero* or through breast milk or saliva up to 3 weeks *post-partum* and (ii) multisystem disease in immunosuppressed patients (Mocarski *et al.* 2007).

Congenital CMV infections (traditionally considered to be transmitted *in utero* or up to 3 weeks *post-partum*) are the major infectious cause of hearing loss and developmental defects in children from western countries (Mocarski *et al.* 2007; Grosse *et al.* 2008), where congenital CMV infection occurs in just under 1% of live births (Dollard *et al.* 2007; Kenneson & Cannon 2007). Whilst only 10% of these children have symptomatic infection at birth, another 10–15% will develop long-term neurological sequelae (Dollard *et al.* 2007; Kenneson & Cannon 2007; Grosse *et al.* 2008). CMV is also a major cause of morbidity in transplant and other immune-suppressed patients causing disseminated multi-organ infections that can be fatal (Mocarski *et al.* 2007). Whilst there have been extensive studies on congenital CMV infections from western countries, establishing the mode of transmission and defining pathogenicity in neonates and immune-suppressed patients, very little information is available from sub-Saharan Africa.

There are data from the USA on congenital CMV infection in the context of maternal HIV, showing that there is a higher prevalence of congenital CMV overall associated with maternal HIV (Chandwani *et al.* 1996; Doyle *et al.* 1996; Kovacs *et al.* 1999), particularly in mothers yet to initiate antiretroviral therapy (Frederick *et al.* 2012). Impaired immunity in HIV-infected women correlates strongly with increased HIV viral load and increased shedding of CMV (Clarke *et al.* 1996; Lurain *et al.* 2004; Schoenfisch *et al.* 2011), and HIV-infected and exposed infants suffer worse outcomes (Kovacs *et al.* 1999). The most damaging congenital CMV infections in western countries were associated with maternal primary infection (Stagno *et al.* 1982), and as the seroprevalence of CMV among African women of child baring age is very high (Manicklal *et al.* 2013), it was perceived that most congenital infections would be asymptomatic and only in rare instances would they have severe outcomes.

The first study on congenital CMV from sub-Saharan Africa reported a prevalence of 1.4% in a cohort of 2032 neonates from the Ivory Coast (Schopfer *et al.* 1978), although this is likely an underestimate as the researchers limited their screen to the first 12 h *post-partum*. Then in 1991, a study was conducted in the Gambia, including longitudinal follow-up of the congenitally infected infants (Bello & Whittle 1991). These researchers were able to culture CMV from either urine or saliva in an alarming 14% of live births. 8% (2/25) of congenitally infected children were born with signs of neurological damage. Both these symptomatic children failed to reach growth milestones and developed partial hearing loss. One had cortical blindness, and the other died suddenly at 1 year of age. A second study from the Gambia detected congenital CMV in 5.4% of live births and did not

document neurological sequelae, but pre-term neonates and those symptomatic or requiring referral were excluded (van der Sande *et al.* 2007). None of these three studies evaluated maternal or infant HIV status with respect to CMV infection.

HIV-infected and HIV-exposed children suffer from impaired physical and mental development (Makasa *et al.* 2007; Manno *et al.* 2012), and the population of HIV-exposed children is growing with the success of prevention of mother-to-child-transmission (PMTCT) programmes (Filteau 2009). A recent study from Zambia showed that early infant CMV infections were both highly prevalent (83% seropositive by 18 months of age), and independently linked with impaired growth overall, and impaired psychomotor development in HIV-exposed children (Gompels *et al.* 2012). This study recruited children at 6 months of age, and so it was not possible to determine how many of these early infant CMV infections were transmitted congenitally. A subsequent Zambian study reported an overall congenital CMV prevalence of 3.8% among admitted neonates (Mwaanza *et al.* 2013), but more importantly, they found that the prevalence among HIV-exposed neonates was more than five times higher than among HIV-unexposed, with 40% of cases being symptomatic. A South African study limited to children born to HIV-infected women detected congenital CMV in 2.9% of children. It also found that a CD4 count <200 cells/μl was associated with increased odds of congenital CMV infection and that lower CD4 counts correlated with higher CMV viral loads in infant's saliva (Manicklal *et al.* 2014). Recent studies from Brazil, another high CMV seroprevalence population (although with lower HIV prevalence), have shown that congenital CMV due to maternal reactivation or re-infections is both highly prevalent (Mussi-Pinhata *et al.* 2009) and causing hearing loss (Yamamoto *et al.* 2011).

The significance of neonatal CMV infections for child health is potentially far-reaching. Obtaining specific funding for CMV studies in the African context may be challenging due to competing priorities for major killer infections. With a growing awareness of the importance of congenital CMV infection in high CMV seroprevalence populations (Manicklal *et al.* 2013), those conducting longitudinal paediatric studies in high HIV burden settings where growth and psychomotor development are outcomes should consider testing for congenital and/or early infant CMV infection.

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