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Declining Maternally-Derived Measles Antibodies in Infants and Nursing Mothers in Nigeria: A Review

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Summary

Measles, also reffered to as rubeolais an endemic respiratory disease caused by a virus. It is a highly contagious infection which typically begins with a mild to moderate fever, often accompanied by a persistent cough, runny nose, conjunctivitis and sore throat. Today, despite the availability of a safe, effective and relatively inexpensive vaccine for more than 40 years, measles still kills more than any other vaccines preventable disease among children. In Pregnant women, IgG immunoglobulin antibody is produced and crosses the placenta to developing fetus' blood circulation; thereby conferring primary protection against infections in the early life of newborns. The presence or absence of Maternal Measles Antibody (MMA) in infants is therefore a factor to be considered in immunization of infants against measles. In Nigeria, the recommended age for routine measles vaccination for infants is at 9 month of age. However, it has been severely reported that the present-day civilized mothers are more measles vaccine-immuned contrary to been natural measles virus-immuned and as such, produce low titer anti-measles virus antibody which consequently decays or clears from their respective infants earlier than 9 months of age when measles vaccine is routinely administered. Early immunization against measles may potentially minimize the duration of the period between the loss of maternal antibodies transferred via the placenta and the administration of the recommended measles vaccination for infants, hence the need for the re-evaluation of the measles immunization schedule.

Keywords: Vaccination; Maternal Measles Antibody; Infant, Virus;

Introduction

Measles is a highly contagious, serious disease caused by a virus. The virus is a spherical, enveloped, single-stranded, negative-sense RNA virus and it is mostly transmitted through direct contact and the air [1]. Measles is a human disease and is not known to occur in animals [2]. The first sign of measles is usually a high fever, which begins about 10 to 12 days after exposure to the virus, and lasts 4 to 7 days. A runny nose, a cough, red and watery eyes, and small white spots inside the cheeks can develop in the initial stage. After several days, a rash erupts, usually on the face and upper neck. Over about 3 days, the rash spreads, eventually reaching the hands and feet. The rash lasts for 5 to 6 days, and then fades. On average, the rash occurs 14 days after exposure to the virus (within a range of 7 to 18 days) [2]. Measles is still common in many developing countries particularly in parts of Africa and Asia. The overwhelming majority of measles deaths occur in countries with low per capita incomes and weak health infrastructures [2].

Among the several antibodies produced in human body, IgG immunoglobulin is the only one that crosses the placenta in pregnant women to developing fetus' blood circulation; thereby conferring primary protection against infections in the early life of newborns [3]. Such passively acquired antibodies from mothers herein referred to as Maternal Measles Antibodies (MMA) is of specific health significance [4,5]. Besides conferring innate immunity against infections in early life of newborns, they have also been reported to impact response of infants to vaccines [6,7]. The efficiency of trans-placental and amount of IgG transferred to fetus depend on the total concentration of IgG in mother, the type of vaccine, The time between vaccination of the mother and delivery, the gestational age of the fetus at birth and the concentration of vaccine-specific IgG and IgG subclasses in mothers [8,9].

It has also been revealed that the present-day civilized mothers are more measles vaccine-immuned contrary to been natural measles virus-immuned and as such, produce low titer anti-measles virus antibody which consequently decays or clears from their respective infants earlier than 9 months of age when measles vaccine is routinely administered [10-12]. However, Sato et al. had earlier reported that the passively acquired anti-Measles Virus IgG (MMA) in neonates is subjected to an exponential clearance rate with a half-life of 35 to 40 days [13]. This might be responsible for two reasons: firstly, when the MMA is absent or present below protective levels in neonates, such are susceptible to measles virus infection; secondly, when present at

considerable titer, the MMA inhibits immune response to vaccine antigens following immunization.

Therefore, it is only after the MMA level is reduced to a significant level in infants, at about 6 to 9 months of age, that vaccine antigens can be given to them to induce effective adaptive immunity. The presence or absence of MMA in infants is therefore a factor to be considered in immunization of infants against measles. In Nigeria, the recommended age for routine measles vaccination for infants is at 9 month of age; however, whether or not this is the right time remains an issue of concern. This study tends to review the emerging reports on the declining anti-measles virus IgG antibody in nursing mothers and their infants presented for routine measles immunization in health centers across Nigeria.

Measles Virus: Structure, Transmission and Pathogenicity

Measles virus is a Paramyxovirus (spherical enveloped particles that contain a non-segmented negative strand RNA genome with a linear arrangement of genes) [2,13,14]. It is a highly contagious acute viral infection having a negative strand RNA virus in the Morbillivirus genus of paramyxoviridae family [14]. Measles virus has two glycoproteins spikes that are important in pathogenesis: fusion protein, which is responsible for fusion of virus and host cell membranes, viral penetration as well as haemolysis. The other protein is the haemagglutin in protein, which is responsible for binding of virus to cells [14,15]. Measles virus has only one serotype i.e. Lifelong immunity occurs in individuals who have had the disease. It has an antigen called Hemagglutinin against which neutralizing antibody is formed [14].

The highly contagious virus is spread by coughing and sneezing, close personal contact or direct contact with infected nasal or throat secretions [2,15]. The virus remains active and contagious in the air or on infected surfaces for up to 2 hours. It can be transmitted by an infected person from 4 days prior to the onset of the rash to 4 days after the rash erupts [2]. It is primarily a childhood disease that is highly contagious with high morbidity, disability and mortality [16]. Measles outbreaks can result in epidemics that cause many deaths, especially among young, malnourished children. In countries where measles has been largely eliminated, cases imported from other countries remain an important source of infection [14].

In humans, measles virus attacks the cells lining of the upper respiratory epithelium of the nasopharynx and spreads to the regional lymph nodes, after 2-3 days of replication in these sites, a primary viraemia widens the infection to the reticuloendothelial system where further replication takes place [2,14]. Secondary viraemia occurs and the virus enters the skin, conjunctiva, respiratory tract and other organs which then lead to further replication. Continuous invasion of this virus leads to the appearances of rash and subsequent formation of multinucleated giant cells [14,15]. The clinical feature of measles is characterized by four notable stages namely; the incubation phase which starts from 10 till 14 days after infection. This is followed by the prodromal phase which begins with fever, malaise, cough, coryza, and conjunctivitis. Koplik spots appear on the buccal mucosa 1-2 days before rash onset and may be noticeable for an additional 1-2 days after rash onset [14,17]. The next phase is followed by the appearance of Maculopapular rashes which occur at 5-7 days after symptoms and lasts 3 or more days with brownish hue which progresses from face to body to extremities and lastly, the convalescent phase which is the gradual return to health and strength after measles illness [14].

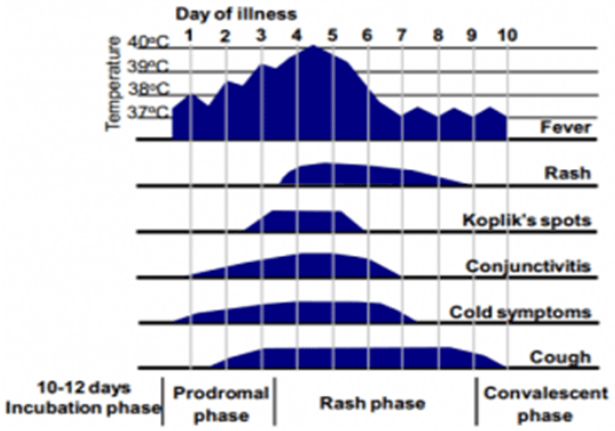

Figure 1: Clinical features of a typical measles virus from onset of illness [14].

Routine Immunization Practices in Nigeria

Nigeria's population skyrocketed from year to year from 155, 207, 145 in 2009 to 186, 987, 563 in 2016 [18,19]. Immunization and vaccination are two of the most important public health interventions and constitute a cost effective strategy to reduce both the morbidity and mortality associated with infectious diseases. Despite this fact, vaccine-preventable diseases remain the most common cause of childhood mortality with an estimated three million deaths each year [20]. Globally, due to the implementation of measles vaccination policies, the mortality rate attributed to measles has decreased between 2000 and 2008 by 78%. During 2008, there were 164,000 deaths attributed to measles globally, which account for approximately 450 deaths per day or 18 deaths per hour. More than 95% of measles deaths occur in low income countries with insufficient health care infrastructures [21]. Nigeria as a country is faced with various challenges such as communal conflicts, widespread corruption, food insecurity, poverty, very weak institutions among others [22,23]. These have made the country to be poorly equipped and positioned to fight effectively the real public health threat [22,24].

In 2008, approximately 83% of the pediatric population globally received one dose of measles vaccine by their first birthday through routine health services which is observed to be notably increased from the respective rate of 72% during 2000. Approximately 700 million children aged from 9 months to 14 years, residing in high risk countries were vaccinated from 2000 to 2008 [25]. An updated estimate by the World Health

Organisations revealed that in 2016, about 85% of the world's children received one dose of measles vaccine by their first birthday through routine health services – up from 72% in 2000. During 2000-2016, measles vaccination prevented an estimated 20.4 million deaths making measles vaccine one of the best buys in public health [2]. In 2016, there were 89,780 measles deaths globally, marking the first year measles deaths have fallen below 100,000 per year [2].

The combined live attenuated measles-mumps-rubella vaccine (MMR), administered at ≥ 12 months of age was introduced in the U.S.A. in 1982 while in Europe, the MMR was introduced in 1988 and has been included ever since in WHO's Expanded Program on immunization, in which Nigeria is benefitting from [26]. The optimum age for measles vaccination varies from country to country, thus, a standardized vaccination schedule is controversial [27]. While the increase in measles vaccination coverage has produced significant changes in the epidemiology of infection in developing countries, measles health problem, with a significant number of infections occurring earlier than the 9 months [28]. In European countries, the first dose of the MMR is administered between 12-18 months of age e. g in France, an early start is recommended for children attending day-care (first dose at 9 months, followed by second dose at 12-15 months), in Germany, following the introduction of the MMR vaccine, both doses are administered during the second year of life [17,27].

The National Program on Immunization in Nigeria stipulates that children be vaccinated against measles by a single injection at 9 months [3,12]. However, persistence of maternal antibodies has been correlated with vaccination failure among infants less than a year of age, thereby making a mockery of vaccination of infants under the age of one year [29]. In addition, most countries recommended vaccination prior to travelling to regions known for the endemicity of the wild-type virus; the first vaccination dose is administered at 9 months of age while the second dose is usually administered 3 to 10 years later. According to the Federal Ministry of Health in Nigeria, a child is considered fully vaccinated if he or she has received a BCG vaccination against tuberculosis; three doses of PENTA to prevent diphtheria, pertussis (whooping cough), tetanus, hepatitis and haemophilus influenza type B, at least three doses of polio vaccine; one dose of measles and yellow fever vaccine [30].

All these vaccinations should be received during the first year of life to confer passive immunity on the child, over the course of five visits, including the doses delivered at birth. According to this schedule, children aged 12–23 months would have completed their immunizations and be fully immunized [30]. To keep track of the delivery of these immunizations, Nigeria also provides parents or guardians with a child immunization health card on which each dose is recorded [30]. In Nigeria, as at the end of 2015, evidence of epidemiologic shift over the years with increased cases in the 5-10yrs cohort shows that 22,567 suspected cases of measles and 112 deaths were recorded from 36 States of the Federation and Federal Capital Territory compared with 15,497 suspected measles cases with 85 death from 36 States reported at the same period in 2014 while confirmed Measles cases in 2015 were 7592 cases [2,30]. However, routine immunization coverage for most LGAs/wards remains suboptimal i.e. less than 80% [30].

In a recent study conducted in Oni Memorial Children's Hospital, Ibadan, South-Western Nigeria, (Onoja, et al.) confirmed that measles was still a major childhood problem that caused high morbidity and mortality in Nigeria [3]. In Ogun State, Nigeria, for example, as at December 2015, the surviving infant's protection level due to measles vaccination was well over 100% (using 2006 Population census) with backlog of un-immunized children across the 20 Local Government Areas. This survey targeted at Abeokuta metropolis which comprised of Abeokuta North and South with the surviving infants/under 1 year (calculated as 4% of total Population using 2006 census population) of 22,380 cumulatively while the protection level due to measles vaccination stands at well over 100%. This coverage resulting from 2006 census population as denominator factor depicts backlog of missed children i.e. lots of surviving infants that were not captured in the vaccination exercise [31].

Table 1: National Immunization Schedule in Nigeria

Minimum Age of Child	**Type of Vaccine**			
At Birth	BCG (given preferably at birth)	OPV 0 (given before the age of 2 weeks).	HepB birth (given within 24 hours after birth).	
6 weeks	OPV1	PENTAVALENT (DPT, Hep B and Hib) 1	Pneumococcal Conjugate Vaccine (PCV) 1	
10 weeks	OPV 2	PENTAVALENT (DPT, Hep B and Hib) 2	Pneumococcal Conjugate Vaccine (PCV) 2	
14 weeks	OPV 3	PENTAVALENT (DPT, Hep B and Hib) 3	Pneumococcal Conjugate Vaccine (PCV) 3	IPV
6 months	Vitamin A supplement			
9 months	Measles		Yellow Fever	

Naturally acquired Trans-Placental Immunity Conferred by MMA

Antibodies are immunoglobulin molecule that has the specific amino acid sequence through which it interact with the antigen that induce its synthesis. Of the antibodies produced in human body, IgG immunoglobulin is the only one that crosses the placenta in pregnant women to developing fetus' blood circulation; thereby conferring primary protection against infections in the early life of newborns. Such passively acquired antibodies from mothers herein referred to as Maternal Measles Antibodies (MMA) are of specific health significance [3]. IgG antibodies are transferred from the mother to the fetus by an active transport mechanism beginning at approximately 17 weeks of gestation and most often following the 28th week of pregnancy. Cord blood values are similar to maternal titres at approximately 33 weeks of gestation and are observed to be 1.5-2 times higher at term [9].

Studies have shown that children with naturally acquired immunity often have significantly higher antibody titer than children with vaccine induced immunity [32]. However, as shown from previous studies, these antibodies impede the response to measles during infancy. The interval between the loss of protection due to the diminishment of maternal antibodies and the protection provided by vaccination should be as brief as possible, particularly secondary to the potential risk of early infection [4]. Infants typically receive the first dose of vaccine around the first year of age. Maternally derived antibodies provide the primary protection for infants prior to this first vaccine dose [33]. The initial concentration of maternal antibodies in a newborn is highly correlated with the antibody concentration in their mother [34].

Subsequently, there is waning of the maternal antibody levels in the infant, leaving the child susceptible to infections. The optimal timing of the first MMR vaccine dose depends on two major factors:

a) The infant's immune system: This should be sufficiently mature to respond to the vaccine antigens.

b) The levels of maternal antibodies must be low enough to ensure that they do not neutralize the live, attenuated strains in the vaccine. Insight in the kinetics and determinants of maternal antibody concentrations is therefore very important [35].

A known determinant of the maternal measles virus antibody concentration is the vaccination status of the mother. Mothers who received Measles vaccine tend to have a lower concentration of measles virus–specific antibodies than mothers who naturally acquired measles [36]. Infants born to measles-vaccinated mothers are hence likely to have lower levels maternal antibodies at birth and a shorter period of protection than infants of mothers who acquired measles naturally [37].

In countries with high MMR vaccination coverage, such as the Netherlands and the United States, most women of childbearing age are vaccinated against measles and have avoided natural infection. A lower duration of protection by maternal antibodies against measles might provide a motivation to lower the age at which the first dose of measles vaccine is administered to infants, but the degree and duration of immune response is uncertain when the vaccine is administered to infants aged < 12 months [37]. Until recently, maternal measles antibodies are transferred via the placenta to the fetus from the mothers among whom either immunity was acquired by natural infection or had repeated natural boosters through contact with the circulating wild-type virus [38].

In a prospective cohort study among 218 women, (Leuridan, et al.) concluded that 10% of naturally infected women and 20% of vaccinated women had no detectable measles IgG antibodies at childbearing age [36]. While mean antibody levels were not differentially associated with participants' age, naturally infected women had significantly higher antibody levels than vaccinated women. In another prospective study of a cohort consisting of 118 children, (Klingeet, al.) provided evidence indicating that only 5% of German infants older than 9 months of age had detectable antibodies against measles. However, the study carried out by (Leineweber, et al.) [9,38] which evaluated prospectively a cohort consisting of 71 full term and 101 preterm infants between 6 to 12 months of age revealed that less than 20% of the infants born after 32 weeks of gestation had detectable measles antibodies. In contrast, all of the infants born prior to 32 weeks of gestation were found to be negative for the presence of measles antibodies.

Also, in a study conducted among 138 infants, (Jo, et al.) reported that the seropositivity rates, as well as the measles specific IgG level decreased rapidly following 3 months of age [39]. This is also supported by a prospective study of maternal measles immunity in a cohort of 147 newborns conducted in Bangladesh [40]. In their study, only 25.5% of the newborns examined had protective levels of measles antibodies between 2-5 months of age and none had protective levels from 5 months onwards. This situation is similar, if not worse in developing countries where infants lose maternally acquired antibodies more rapidly than those in developed countries.

Declining rate of MMA in Nigeria

It is noteworthy that infants in developing countries may lose maternally acquired antibodies as early as age 5 to 6 months [41]. Unfortunately, vaccination against measles in one generation increases the possibility of infection in the next. As time passes, the proportion of vaccines in the population increases, with the latter gradually replacing individuals with lifelong protection acquired from natural infection. Infants become more susceptible as passively acquired maternal antibodies become less and are catabolized earlier [42].

A study conducted in Ibadan, Nigeria by (Adu, et al.) determine the role of the presence of measles antibodies (MV) in the serum and breast milk of lactating mothers revealed that only 2.0% of the 396 children brought to the health facility for routine measles vaccination had MV antibodies in their sera prior to vaccination as against 20.2% of their mothers in either breast milk or sera [43]. They observed that the low seroconversion rate observed in their study could be attributed to the low potency of the vaccines used rather than the presence or absence of MV antibodies in the sera or breast milk of mothers. This reported is directly linked

to the fact that vaccine-induced immunity is less robust and less durable than immunity conferred by natural infection. Moreover, it is possible that the diminishment of antibodies is accelerated in the absence of re-exposure to wild-type virus and, therefore, lacks natural boosting immunity [27].

In a study conducted by (Hartter, et al.) only 17% of the 4-month-old Nigerian infants were protected against measles [41]. The report revealed that the overall prevalence of measles antibodies of 206 infants up to 9 months of age was 45% and the prevalence of measles antibodies was limited to 32% among infants aged 3 months and 2% among those aged 6-9 months. In another study carried out in Osogbo, Nigeria on MMA, all the 9-months infants tested, 84 of 84 (100%) were seronegative and susceptible to Measles [12]. Similar result was reported in Abeokuta, Nigeria by Adebari that all the Nursing mothers (92) evaluated for the presence of maternal measles IgG (MMA) produced low titre of anti-measles virus IgG antibody [44]. He also reported a decline in the anti-measles virus IgG antibody from their respective infants when presented for measles immunization at 9 months.

By implication, all the infants tested in the study reviewed were at the time of presentation for measles virus containing-vaccine susceptible to measles infection. These studies also revealed that there is a decrease of natural boosting effect of the wild-type measles virus and that many nowadays mothers become immune through measles vaccination. Measles vaccine induces lower antibody titers in mothers who consequently transferred low titer measles virus antibodies to their infants with resultant early loss of such usually before 6 to 9 months of age compared to natural measles immune mothers and their infants [4,36]. The outcome of the undetectable antibodies and some low titer across the groups especially when it is noted that all children have received measles vaccination at 9 months of age indicates a possibility of some primary vaccine failure, which could be due to persistence of maternal antibodies or improper storage and handling of vaccine receipt of immunoglobulin, genetic factors and other incompletely understood factors or cases of non-vaccination or religious or political objections [27,45-49]. A person who shows a certain attitude towards something is reacting to his conception of that thing rather than to its actual state [50]. This therefore calls for the need to improve surveillance and review the immunisation programs.

A study was conducted by (Olaitan, et al.) in Kaduna, the northern part of Nigeria, to compare the sero prevalence of measles virus immunoglobulin maternal antibodies in children aged 0–8 months and a control population aged 9-23 months presenting with measles-like symptoms in selected hospitals in Kaduna State [17]. A total of 273 blood samples comprising 200 from children aged 0-8 months and 73 from children aged 9-23 months were collected and analyzed for measles virus IgM antibodies by enzyme-linked immunosorbent assay. The results showed that the prevalence of measles virus increased with age in children aged 0-8 months and decreased with age in older children aged 9-23 months, showing a significant association between measles virus and age of the child. Similar results were reported in AkwaIbom, an eastern state of Nigeria and inBorno, a northern statein Nigeria [5,51].

Hence, the confirmation of the presence of measles virus infection in children aged 0-8 months. Since the presentation of Infants for measles vaccination in Nigeria is at 9 month, the absence of MMA from reports reviewed revealed that the children are due for measles immunization. However, from another perspective of susceptibility, more so in case they had lost the MMA some months before they clock 9 month, one might say the presentation of the infants for Measles vaccination at 9 month-old was inappropriately delayed. The infants should have been presented earlier to protect them against possible exposure to wild-type measles virus which more often than not results in high morbidity and mortality in non-immune children.

Early Vaccination as a solution to rapid decline of MMA in susceptible infants

Early immunization against measles may potentially minimize the duration of the period between the loss of maternal antibodies transferred via the placenta and the administration of the recommended measles vaccination for infants [52]. In developing countries such as Nigeria, vaccination against Measles Virus (MV) is generally administered at 9 months of age. Although it is well-documented that protection of most infants by passively acquired maternal MV antibodies is waning before immunization is given; it is imperative that more drastic measures regarding vaccination are taken. In a study conducted in Ilorin, Kwara State, Nigeria by (Fowotade, et al.) to assess the low levels of pre-vaccination measles antibody among infants receiving measles immunization, a larger proportion (53.8%) of the children had no detectable anti-measles virus antibody while 39.0% had low (non-protective) titer; these put both groups at risk of developing measles given the endemic nature of Nigeria [27,41,44]. They therefore recommend a re-evaluation of 9 months as the age for measles vaccination in Nigeria vis-à-vis 92.8% with < 40 HI titer is highly recommended.

Specifically, it is suggested that a two-dose measles vaccination policy, with a first dose of monovalent vaccine administered at 6 months of age may be implemented in Nigeria [41]. Their findings on the comparative study on decay of passively acquired Measles Virus antibodies in newborn gives twice as high Anti-Measles Virus IgG titers as in German newborns than the Nigerian newborns. This occurred even more rapidly than expected resulting in susceptibility to Measles Virus in most of the 4-month-old infants in Nigeria. Furthermore, transfer of maternal anti-Measles Virus IgG to the newborn was more efficient in the German cohort compared with the Nigerian group. The findings suggest the use of alternative vaccination strategies in developing countries to possibly reduce the window of susceptibility against measles [41].

Several studies concerning vaccination with combined MMRV have also shown that administering the vaccine in infants as early as 9 months of age with a second dose administered at 12 months of age results in good immunogenicity. Therefore, the vaccine can be used in circumstances where early protection is needed [53].

However, there exist potential barriers to the adoption of earlier immunization schedules, including the inherent immaturity of the immune system of young infants, as well as the potential interference by maternal antibodies. It is important to note that the main determinant of maternal antibody-mediated inhibition of immune responses is represented by the titre of maternal antibodies present at the time of immunization, or rather by the ratio of maternal antibodies to vaccine antigen administered. It is thus possible that late immunization might be more efficient than early immunization even in the presence of maternal antibodies.

However, such a strategy would fail to prevent early cases of infection, which are concomitantly most often of greater severity. This observation might due to the fact that trace amounts of maternally transferred neutralizing antibodies are not detected with the commonly used serological methods and interfere with the sero-conversion. Also, the immune system of 6 month old infants may not be mature enough to mount a sufficient antibody response to vaccination. Therefore, DNA vaccines that express viral proteins could potentially serve as the solution to providing adequate protection among newborns and young infants from severe illness during the period of elevated disease susceptibility. This would still allow for a boost immunization with the live attenuated measles virus vaccine, as recommended, after 9 months of age.

Conclusion

A more comprehensive understanding of measles immunity in infants would enhance the use of already existing live attenuated measles virus vaccines and their administration to younger infants. However, nursing mothers needs to practice exclusive breastfeeding as well as present their children earlier for the first dose of measles vaccine. However, the Government should consider the introduction of a second dose as a booster dose to increase the herd immunity of all eligible children, hence, the need to improve surveillance and review the immunisation programs.

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