A sero-survey to identify the window of vulnerability to measles in infants in north-eastern Nigeria

Baba Usman Ahmadu (Consultant Paediatrician), Garba Ashir (Consultant Paediatrician and Senior Lecturer), Modu Mustapha (Consultant Paediatrician and Senior Lecturer), Yakubu Mava (Consultant Paediatrician and Senior Lecturer), Isa Saidu (Registrar (Paediatrics)) & Jose Ambe (Consultant Paediatrician and Professor)

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A sero-survey to identify the window of vulnerability to measles in infants in north-eastern Nigeria

BU Ahmadu, GM Ashir, MG Mustapha, Y Mava, IH Saidu, JP Ambe

Introduction

Since the introduction of an inexpensive and highly effective measles vaccine in the 1960s and the global prioritisation of measles control initiatives, the burden of the disease has significantly reduced worldwide. In 1997, there were 36 million cases, and more than one million deaths occurred worldwide, but measles now accounts for an estimated 164,000 deaths per year globally. Yet, it still persists as a public health threat. In Africa, the number of cases increased from 36,000 in 2009 to 172,824 in 2010, and outbreaks were reported in countries with successful measles control programmes. During a two-year study, Ashir et al reported 11.2% cases of measles in Maiduguri, Nigeria in 2009. A notable proportion of measles occurs in infants before the age of nine months, which is the age at which the measles vaccination is currently recommended in most developing countries. The occurrence of measles in these infants results from numerous factors, including the high transmissibility of the measles virus and increasing rates of vaccine refusal because of ignorance and socio-cultural beliefs, especially in developing countries, which deprive children of access to immunisation services. The current measles vaccine does not elicit high antibody levels when administered to infants who are younger than nine months of age. Maternal measles antibodies (MMAs) that are still present in infants could neutralise the measles vaccine, thereby making it ineffective before one year of age. Finally, while MMAs, at adequate levels, can protect infants early in life, multiple factors influence the quantity of measles antibodies that cross the placenta to the foetus.

As a result, for several months many infants are vulnerable when their MMAs fall below protective levels against the measles virus. At the same time, these low MMAs may interfere with antibody production in response to the measles vaccine. During this window of vulnerability, young infants may develop severe or fatal measles, if exposed to the measles virus. In the 1990s, vaccination of six-month-old infants with a high-dose measles vaccine was explored as a strategy to overcome MMAs and enable successful measles immunisation of infants during this window period.

However, excess mortality in female infants, which was believed to be as a result of their low antibody-dependent cellular cytotoxicity response, led to abandonment of that approach. The decision to forsake the use of a high-dose measles vaccine may have been too hasty because excess female mortality in recipients of the high-dose measles vaccine was not a consistent finding. In the 1990s, vaccination of six-month-old infants with a high-dose measles vaccine was explored as a strategy to overcome MMAs and enable successful measles immunisation of infants during this window period. A possible explanation for this finding could be the presence of MMAs...
in that study population prior to administration of the high-
dose measles vaccine, as excess mortality was observed in
female subjects with undetectable MMAs prior to measles
immunisation. Absence of MMAs may result in greater
measles virus replication following immunisation, putting
these infants at greater risk of events that are associated
with immunosuppression. Factors that are associated with
low cellular-mediated immune response, namely female sex,
high-titre vaccine and early age, are not restricted to measles
vaccines alone. These factors have also been associated with
lower survival rates in other vaccine-preventable diseases.11,12

The primary strategy, now being pursued to control the
measles burden in developing countries mostly, is based on
mass measles immunisation campaigns that target infants
and older children. By drastically diminishing the incidence of
measles in a susceptible population, it is hoped that infants
will be indirectly protected. An adjunct control strategy aims
to immunise infants who are less than six months of age with a
new generation of measles vaccine in developing countries. In
support of this strategy, the Bill and Melinda Gates Foundation
has sponsored initiatives to develop measles vaccines that can
be safely administered in early infancy.13 The new vaccines
may supplement what can be accomplished with the current
measles vaccines. Information on the prevalence of MMAs at
different time intervals in infancy is needed to help to guide
the development of these new vaccines.

Method

Our prospective hospital-based cohort study was carried out
on newborn infants at the Paediatrics and Obstetrics Units
of the University of Maiduguri Teaching Hospital (UMTH),
north-eastern Nigeria, between 10 January 2010 and
21 July 2011. The UMTH serves as a referral site for the
region and the neighbouring countries of Chad, Cameroon and
Niger. Ethical approval was obtained from UMTH’s Medical
Research and Ethics Committee. Informed consent was also
obtained from parents. The subjects were selected using the
systematic random sampling method whereby the first of
every three newborn infants was selected at the labour ward.
Two millilitres of umbilical cord blood were taken from the
newborn infants to quantify the MMAs. Subsequently, during
each infant’s visit at six weeks, three months, six months and
nine months of age, 2 ml of venous blood was obtained from
the infant to analyse the MMAs. Collected blood samples
were centrifuged and the serum was stored at -20°C until the time
of assay.

Demographic variables and medical history, including a
history of measles, contact with suspected measles and a
history of transfused blood, were collected during enrolment
and subsequent visits. Samples were assayed individually
for MMAs using enzyme-linked immunosorbent assay in
accordance with the standardised laboratory procedure to
determine the MMAs.14,15 The optical densities of reactions in
the well plates were read in an automated analyser at 450
nanometre wavelength. MMA titres were obtained by plotting
graphs of optical densities against measles immunoglobulin
G concentrations. Protective titres for MMAs were defined as
levels of MMAs > 12 U/ml and unprotective titres as levels of
MMAs ≤ 12 U/ml, similar to that mentioned in a publication
by Joshi and Gambhir.16

Data were analysed using SPSS® statistical software version
16 (Illinois, Chicago USA). Values were expressed as mean ±
standard deviation (SD). The mean coefficients were
compared using Student’s t-test. The chi-squared (χ²) test
was employed where appropriate to determine associations
for the qualitative variables. A p-value < 0.05 was considered
to be significant based on the sample size estimate of current
study subjects. Tables were used for illustrations.

Results

Table I shows that a total of 77 infants at birth were followed
up to nine months of age. There were 40 male (51.9%) and 37
female (48.1%) infants. This equates to an approximate male
to female ratio of 1.1:1. Nine (11.7%) of the newborn infants
were preterm, 57 (74%) were full-term and 11 (14.3%) were
post-term deliveries, respectively. The majority of the newborn
infants (73, 94.8%) had protective MMAs at birth. The mean
± SD of MMAs of the newborn infants at birth was 216.04
± 72.57 U/ml at 95% confidence interval: 199.57-232.51
U/ml.

Table I: Gestational age and gender distribution of the 77 infant

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm (&lt; 37)</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Full-term (≥ 37 &lt; 42)</td>
<td>28</td>
<td>29</td>
<td>57</td>
</tr>
<tr>
<td>Post-term (≥ 42)</td>
<td>8</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>37</td>
<td>77</td>
</tr>
</tbody>
</table>

Table II shows the proportion of MMA levels of the infants at
different ages in the follow-up cohort. The number of infants
with protective MMAs declined to 36 (46.8%), 28 (36.4%),
13 (16.9%) and 4 (5.2%) at six weeks, three months, six
months and nine months of age, respectively. Sixty-four
infants (83.1%) had unprotective MMAs at six months of age.
The overall decline in the proportion of infants with protective
MMAs from birth to nine months of age was significant
(p-value = 0.000).

Table II: Age distribution of maternal measles antibodies of the newborn

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Maternal measles antibodies (U/ml)</th>
<th>χ²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Protective, n (%)</td>
<td>Unprotective, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>73 (94.6)</td>
<td>4 (5.2)</td>
<td>-</td>
</tr>
<tr>
<td>1.5</td>
<td>36 (46.8)</td>
<td>41 (53.2)</td>
<td>42.982</td>
</tr>
<tr>
<td>3</td>
<td>28 (36.4)</td>
<td>49 (63.6)</td>
<td>1.711</td>
</tr>
<tr>
<td>6</td>
<td>13 (16.9)</td>
<td>64 (83.1)</td>
<td>7.479</td>
</tr>
<tr>
<td>9</td>
<td>4 (5.2)</td>
<td>73 (94.8)</td>
<td>5.356</td>
</tr>
</tbody>
</table>

*: p-value < 0.05 (significant)
The association of mean MMAs from birth up to nine months of age with the gestational age of the newborn infants was insignificant for preterm (p-value = 0.272), full-term (p-value = 0.246) and post-term (p-value = 0.226) deliveries. Similarly, the mean MMAs from birth up to nine months of age had an insignificant association with the gender of the newborn infants for male (p-value = 0.257) and female (p-value = 0.234).

Discussion

Our findings show that the window of vulnerability to measles in infants in Maiduguri begins at six weeks and extends to nine months of age, which is the recommended age for measles vaccination in developing countries. There were significant losses of MMAs at six weeks of age in the current study. This conforms with observations that were made in Ilorin, Nigeria, and with those on Kangaba infants in Mali. However, almost all of the studied infants in Bangladesh had protective levels of MMAs at six weeks of age. This suggests that in the present study, during pregnancy, the mothers may have transferred a lesser, but protective, amount of MMAs via the placenta to their foetuses. Hypergammaglobulinaemia, which reduces the placental transfer of MMAs, could have led to the observed levels of MMAs at six weeks of age in this study. Previous studies have also demonstrated that hypergammaglobulinaemia decreases the placental transfer of MMAs in African mothers, compared to mothers in industrialised countries. Natural infection of mothers with the measles virus, because of the high incidence of measles, was the reason that was advanced for MMAs in infants at six weeks in Bangladesh.

In the present study, at three and six months of age, 63.6% and 83.1% of infants had unprotective levels of MMAs. This is similar to observations that were reported in studies on Nigerian and Argentinean subjects. The most likely explanation for this could be the changing epidemiology of measles, such that MMAs identified in infants today are low, compared to those reported in infants decades ago. Given advances in measles control programmes, which mean that infants now receive less MMAs from their mothers, our study findings (at three and six months) were anticipated.

In our study, at nine months of age, almost all of the enrolled subjects were unprotected against measles. Only 5.2% of them had protective levels of MMAs. This is consistent with the finding of a study that was conducted in France. However, none of the infants who were studied in South Africa had protective levels of MMAs at nine months of age. The reason for this could be a physiological saving mechanism that was present in the infants. It is believed that high levels of MMAs at birth are eliminated rapidly, whereas low levels of MMAs at birth are saved so that they last longer in infancy. Therefore, there was an increased susceptibility to measles in the current study population. In the present study, the loss of MMAs was independent of the gender of the infants, which corroborated observations that have been made by other researchers. Also, in the current study, the decline of MMAs was independent of the gestational age of the infants. Although sample sizes in relation to gestational ages were small in our study and may not be of sufficient power, the findings agree with the observations of a study that was conducted in Atlanta, Georgia. Gestational age could be a factor that influences MMAs at birth, rather than the waning of MMAs in infancy.

In conclusion, our findings suggest that there were protective levels of MMAs in newborn infants at birth. These levels rapidly declined in infancy, irrespective of gender and gestational age at birth. The majority of the infants were unprotected against measles by the age of six months. Together with ample evidence for a high disease burden in susceptible infants, our findings suggest that new, safe and effective measles vaccines to protect these infants should be introduced. A large population-based sero-survey at community level is also needed in Nigeria to further validate this study of public health significance.

Conflict of interest

All authors declare that they have no commercial or other association that might pose a conflict of interest to this article.

Declaration

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References available on request