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By Delfina R. Msanga, Raphael Rwezaula, Semvua Kilonzo, Elizabeth Kwiyolecha, Tulla Masoza, Emmanuel Mkumbo, Mariam M. Mirambo & Stephen E. Mshana

Catholic University of Health and Allied Sciences

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Methodology: A cross-sectional study involving children below five years of age was conducted at Makongoro Reproductive and Child Health (RCH) clinic between May and June 2017. Socio-demographic data were collected, and vaccination status was confirmed from reproductive and child health (RCH) cards. Serum HBV surface antibodies (anti-HBs) were quantified using enzyme immunoassay (Enzygnost Anti-HBs II). Data were analysed by using STATA version 13 software.

Keywords: *hepatitis B, children, immune response, seroconversion, mwanza, Tanzania.*

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Immune Response after Three Doses of Hepatitis B Vaccine among Children below Five Years of Age in Mwanza, Tanzania

Delfina R. Msanga [α], Raphael Rwezaula [σ], Semvua Kilonzo [ρ], Elizabeth Kwiyolecha [ω], Tulla Masoza [¥], Emmanuel Mkumbo [§], Mariam M. Mirambo [χ] & Stephen E. Mshana [ν]

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Results: A total of 300 children were enrolled with the median age of 15 (Interquartile range [IQR]: 9-22.5) months. The median interval from last dose to the time of evaluation was 10(IQR: 5-18) months with all children assessed ≥8weeks post-vaccination. Out of 300 children, 265(88.3%, 95% Confidence interval [CI]:84-91) had ≥ 10IU/L of anti -HBs indicating sero-conversion. The median titres among those who seroconverted was 66(IQR: 26-134) IU/L. The median age at the time of evaluation of those who seroconverted was significantly lower than those who were not seroconverted [14(IQR: 9-21) vs. 18(IQR: 11-26, P=0.03]. The titres were found to decrease significantly by 0.84 and 0.98 IU/L with a unit increase in interval from last dose and a unit increase in age, respectively.

Conclusion: There is high seroconversion after three doses of HBV vaccine among children in Tanzania which is associated with young age. Further studies to evaluate immunogenicity of HBV vaccine in different age groups are recommended in resource limited countries to provide data that regarding booster dose recommendation. In addition, there is a need to evaluate immunization efficiency by determining immunogenicity of one of the vaccine component in the package as a proxy indicator.

Author α σ ω ¥: Department of Pediatrics and Child health, Weill Bugando School of Medicine, Catholic University of Health and Allied Sciences, P.O. Box 1464, Mwanza, Tanzania.

Author § ν χ: Department of Microbiology and Immunology, Weill Bugando School of Medicine, Catholic University of Health and Allied Sciences, P.O. Box 1464, Mwanza, Tanzania.

e-mail: mmmirambo@gmail.com

Author ρ: Department of Internal Medicine, Weill Bugando School of Medicine, Catholic University of Health and Allied Sciences, P.O. Box 1464, Mwanza, Tanzania.

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I. Backgrounds

Hepatitis B virus (HBV) infection is one of the most common diseases across the globe with one third of the population estimated to be infected[1]. About 5% of total world population are chronic carriers and nearly a quarter of these carriers develop liver cirrhosis and hepatocellular carcinoma[2] with about one million deaths being reported annually [3]. Therapeutic options for treating HBV chronic infections are difficult to implement and are not yet fully effective in many settings particularly in resource limited countries. Vaccination remain to be an effective measure to prevent HBV infections. Effective vaccination has been found to reduce HBV infections, therefore reducing the risk of transmission to the susceptible contacts[4]. In the intermediate and high endemic regions, individuals are at high risk of acquiring HBV infection if vaccination is not implemented [1]. The World Health Organization (WHO) recommends that HBV vaccination should be part of national immunization programs for countries with HBV carrier prevalence of 8% or greater, to reach a goal of reducing a proportion of chronic carriers and complications associated with HBV infections [5, 6].

In Tanzania the inclusion of HBV vaccine in childhood immunization program was first implemented in 2013 and the vaccine is administered 0.5ml intramuscular on fatty tissue over anterolateral thigh muscle at weeks 6, 10 and 14 respectively after birth in combination with other 4 vaccines in the package (pertussis, diphtheriae, tetanus and *Haemophilus influenza* type B). It is estimated that this standard schedule of immunization should produce about 95% seroprotection [6]. Despite the reported high seroconversion following HBV vaccination in other countries, there are variations in these proportions among different geographical areas with different endemicity status[7]. A previous study[8] in Dar es Salaam among children below five years of age reported sero-conversion of 69%.

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Different factors including storage conditions, different forms of immunosuppression, genetic makeup etc. have been implicated to affect the immune response to HBV vaccination[9, 10]. In the countries like Tanzania, where there is no routine assessment of immune response which will lead to additional dose for non-responders, there is a need of data to evaluate DPT-HBV programme after 6 years of its implementation. In addition, there is limited data on the efficiency of childhood immunization particularly in vaccines which are given in combinations in Tanzania. Some previous studies evaluated efficiency of childhood immunization by using other components such as diphtheriae and tetanus toxoid (TT) vaccine [11-13] while others used pertussis component. In a view of that, the study was designed to assess the immunogenicity of HBV vaccine among children who completed three doses, the information that may be useful in controlling vaccine preventable diseases in Tanzania.

II. Methods

a) Study design, study area and study population

The cross-sectional study was conducted from May to June 2017 among children under five years of age from Makongoro reproductive and child health (RCH) clinic. This facility had no any report of cold chain problems in routine assessment.

b) Sampling and inclusion criteria

The sample size was calculated using Kish Lisle formula using the prevalence of 87%[14]. Children under five years of age who had received three doses of HBV vaccine (Pentavalent Vaccine-DPT-HepB-Hib) were serially enrolled until the sample size was reached. The study included only children who had received three doses of Pentavalent Vaccine (DPT-HepB-Hib) with the last dose given at least 8 weeks ago. To avoid non-responders due to chronic HBV infection, all children who were HBsAg positive were excluded from the study.

c) Laboratory procedures

About 3ml of venous blood was aseptically collected using plain vacutainer tubes (BD, Kenya, and Nairobi) and transported to BMC accredited laboratory for processing. The anti-HBs titres were quantified using enzyme immunoassay (SIEMENS, Enzygnost® Anti-HBs II, and Germany) following manufacturer's instructions to detect the presence of specific anti-HBs. The presence of anti-HBs greater than 10IU/L was defined as presence of protective antibodies.

d) Data management and analysis

Data were entered and analysed using a STATA version 13. Continuous variables were summarized as median with inter-quartile range and categorical variables were summarized as proportions. Rank sum-Mann Whitney test was used to compare the median titres, weight, age and interval from the last dose. Using immune response as outcome, multivariate logistic regression analysis was done. However, weight and interval were not included in the model because of their collinearity with age. In all children with titres greater than 10IU/L, regression analysis was done to determine the correlation between age, interval from the last dose and titers. A predictor with a *P* value of <0.05 was considered statistically significant.

III. Results

a) Socio-demographic characteristics of the enrolled children

A total of 300 children under five years of age who received three doses of HBV vaccine were enrolled. There was almost equal distribution between females (49%) and males (51%). The median age of enrolled children was 15 (Interquartile range [IQR]: 9-22.5) months. The median interval from last dose to the time of evaluation was 10(IQR: 5-18) months with all children assessed ≥8weeks post -vaccination. The median duration for breastfeeding was 12(IQR:9-15.5) months (Table1). All children had no co-morbidities.

Table 1: Characteristics of enrolled children and seroconversion

Variable	Univariate analysis			Multivariate	
	Positive	Negative	P-value	OR[95%CI]	P-value
Age(months)	14(IQR:9-21)	18(IQR:11-36)	**0.030**	0.96(0.94-0.99)	**0.005**
Breastfeeding duration (months)	12(IQR:9-16)	12(9-14)	0.766	1.29(0.59-2.79)	0.514
Interval from the last dose(months)	10(IQR:5-17)	13(IQR:5-31)	0.103		
Weight(kgs)	9.5(IQR:8.4-11.2)	10.4(IQR:9-13.5)	**0.014**		
Sex					
Female	127(86.4)	20(13.6)			
Male	138(90.2)	15(9.8)	0.305	1.39(0.67-2.87)	0.370

b) Seroconversion and associated factors

Out 300 children, 265(88.3%, 95% Confidence interval [CI]:84-91) had≥ 10IU/L anti -HBs indicating sero-conversion. The median titres among those who seroconverted was 66(IQR: 26-134) IU/L. The median age at the time of evaluation of those who seroconverted was significantly lower than those who were not seroconverted [14(IQR: 9-21) vs. 18(IQR: 11-26, P=0.03] (Figure1).

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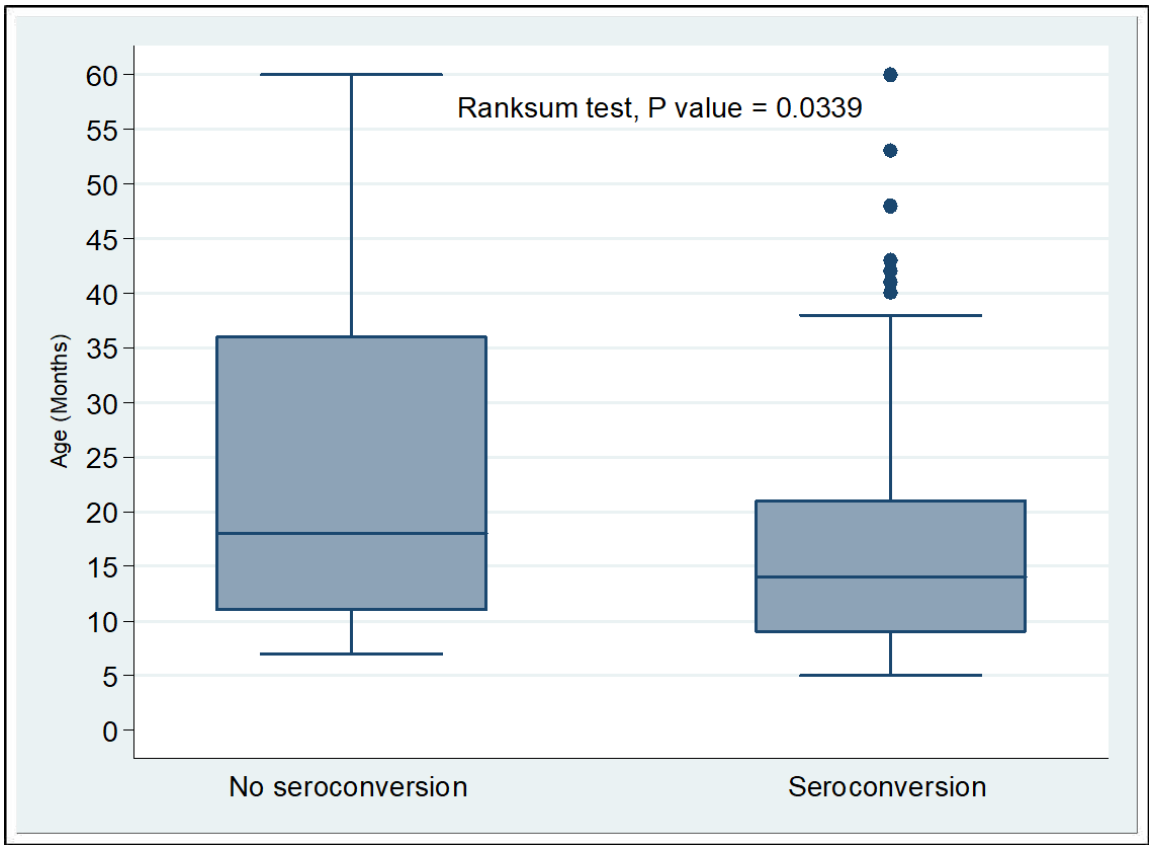


Figure 1: Box plot showing median age of those with seroconversion and those with no seroconversion

By multivariate logistic regression analysis decrease in age was independently associated with seroconversion (OR: 0.96(95%CI: 0.94-0.99, *P*=.005). The titres were found to decrease significantly as the age increases (Coef= -0.96, 95%CI -1.700 - -0.274, *P*=.007) (Figure2).

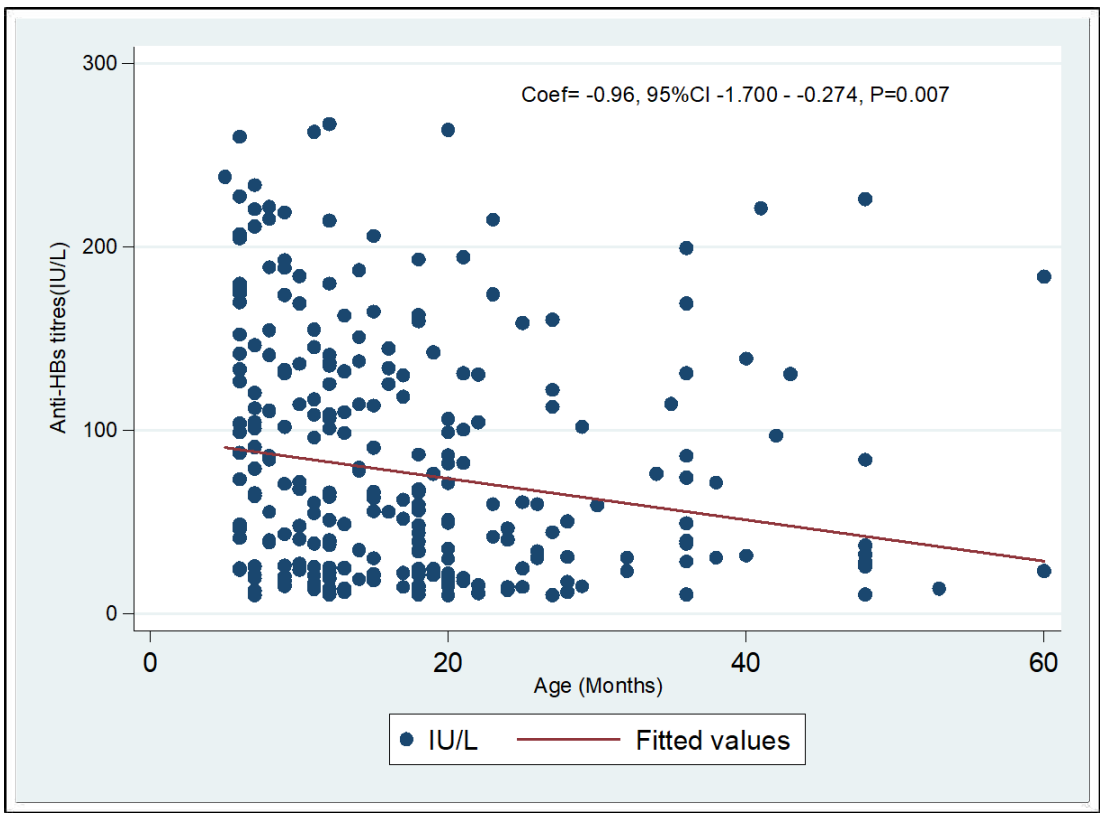


Figure 2: Scatter diagram with fitted line showing correlation between age and anti-HBs titres

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In addition, the titers were also found to decrease as the interval from the last dose increases (Coef= -0.84, 95%CI, -1.591- -0.106, *P*= .025) (Figure3).

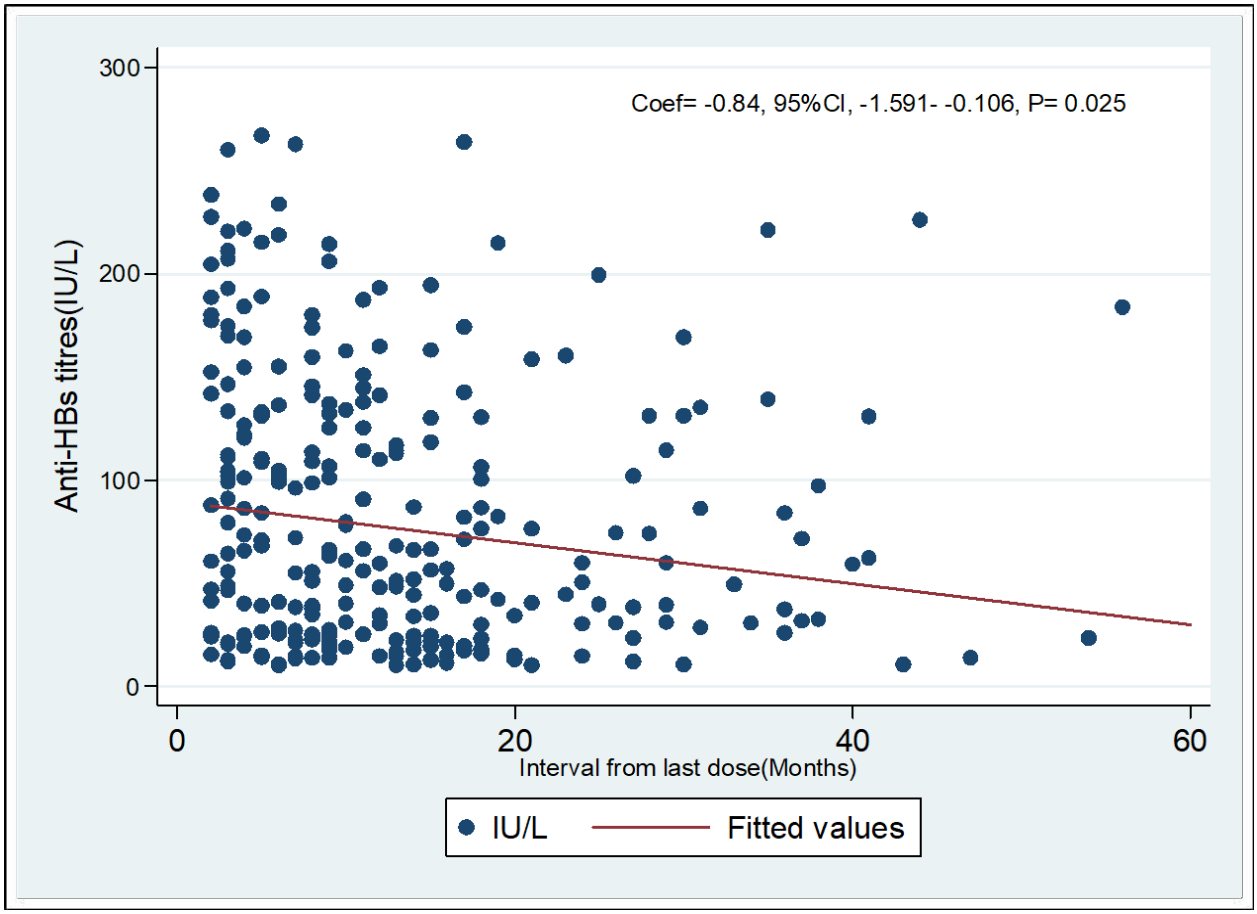


Figure 3: Scatter diagram with fitted line showing correlation between interval from last dose and anti-HBs titres

IV. Discussion

One of the key aspects in vaccination programs in resource constrained countries is to ensure potency of the vaccine by maintaining the cold chain. Therefore, there is a need for regular studies to assess immunogenicity of vaccines especially those which are given in combination to provide a proxy indicator for the efficiency of other vaccines in the package. In Tanzania, HBV vaccine is given in combination with *Corynebacterium diphtheriae*, *Bordetella pertussis* (whooping cough), *Clostridium tetani* (tetanus) and *Haemophilus influenza* type B (influenza). However, there is paucity of data on immunogenicity of these vaccines.

To the best our knowledge, this is the first study to assess immune response after HVB vaccine among children in Mwanza, Tanzania. In the present study about 90% of children seroconverted after three doses of HBV vaccine. The observed high seroconversion and sustained high HBV vaccination coverage of 92.5% [15] reported in Mwanza will eventually reduce the transmission of HBV in future. In addition, this information can be used as a proxy indicator for efficiency of other vaccines given in combination with HBV vaccine in Tanzania. The reported seroconversion rate in the current study is consistent with the previous reports which documented the seroconversion of 87%, 81.5%, 94.1 and 96.7% [14, 16-19]. In the contrary, the reported seroconversion in the current study is higher than reported previously in Dar es Salaam and other endemic areas[8, 20]. Variations in seroconversion might be attributable to the type of vaccine used in terms of synthesis and preparations etc; in the current study the vaccine used was Pentavalent Vaccine (DPT-HepB-Hib) which might be different from other studies where monovalent HBV was used [14, 16]. In addition, amount of antigen delivered, genetic variation among the population involved, vaccination coverage, endemicity status, faults in vaccine cold chain, methods used to evaluate antibody titers etc. might contribute to the observed discrepancies [21-24]. Moreover, in this study, about 11.7% of children were found to be non-responders after receiving three doses of HBV vaccine which is slightly lower than 14.6% and 15.6% reported in previous studies[25, 26]. The possible explanation could be genetic variability and impaired lymphocyte activation as reported earlier [19, 27-29]. It should be noted that children studied in the current study were healthy with

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no co-morbidities. Genetic factors and primary immunodeficiencies could were not ruled.

In the current study, it was observed that, as the age increases by one month, the anti-HBs titers were found to decrease by 0.96 IU/L. It was further observed that, the anti-HBs titers decrease by 0.84IU/L as the interval from the last dose increases by one month. With this trend, by the age of 10 years most of these children would have undetectable levels of anti-HBs titers necessitating the need for considering booster dose to provide long lasting protection. Cohorts with long term follow-ups are recommended in this setting to evaluate the need for a booster dose. This observation is consistent to what was reported earlier [16, 20, 30-32] whereby the anti-HBs titers were found to decrease as the age increases and almost undetectable to a significant proportion of children by the age of 11 years. In the contrary some other studies concluded that, there is no need for booster dose after receiving 3-dose schedule of HBV vaccine since the anti-HBs titers can persist for longer period [33] while another study confirmed that there is long lasting cellular immunity despite decrease anti-HBs levels[34]. This conflicting information could be due to endemicity status in the study areas. Further studies to evaluate the levels of anti-HBs titers and cellular immunity among different age groups are highly recommended in areas with different endemicity status.

Regarding sex, in the current study, there was no significant difference in the levels of anti-HBs titers among female and male children which is similar to the previous reports [14, 25, 35]. This could be explained by the fact that there was almost equal distribution between males and females with equal distribution of factors that could influence seroconversion and level of titres.

Limitations of this study include: Inability to assess other forms of primary immunodeficiencies and genetic conditions which might impair immune response to vaccines and contributes to a significant proportion of non-responders and failure to give birth dose as it is not included in Tanzania Immunisation Vaccination and Development Program.

V. Conclusion

There is high seroconversion after three doses of HBV vaccine among children in Mwanza city which is associated with young age. Further studies to evaluate the level of protective antibodies at different age groups are recommended across the country and other resource constrained countries. This necessary especially in deciding the issue of dose at birth and booster dose in ration to HBV vaccination. High seroconversion of HBV vaccine signifies the effectiveness of other childhood vaccines in Tanzania.

List of abbreviation

Anti-HBs: Antibodies against hepatitis B surface antigen
CUHAS: Catholic University of Health and Allied Sciences
CI: Confidence interval
ELISA: Enzyme-linked immunosorbent assay
HBV: Hepatitis B Virus
HBs: Hebatitis B surface antitigen
IU: International Unit
IQR: Interquartile range
OR: Odd ratio
TT: Tetanus toxoid

Declaration

Ethical approval and consent to participate

The ethical clearance to carry out the study was approved by the joint Catholic University of Health and Allied Sciences/Bugando Medical Centre (CUHAS-BMC) research ethics and review committee (CREC) with ethical clearance number CREC/118/2016. All the parents/guardians were asked to sign informed consent on behalf of their children prior enrollment to the study.

Consent for publication

Not applicable

Availability of data and material

All data were included in this manuscript. The raw data is available upon request to the Director of research and Innovation of the Catholic University of Health and allied Sciences.

Competing of interests

No conflict of interest to declare.

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Authors' contributions

DRM, SK, RR, EK, TM, MMM and SEM participated in the design of the study. EM and DRM participated in the collection of specimens and data. MMM, SEM and EM performed serological tests. SEM and MMM analyzed and interpreted the data. DRM wrote the first draft of the manuscript. SEM and MMM provided a critical review of the manuscript. All authors read and approved the final version of the manuscript.

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