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SHORT COMMUNICATION

Insufficient measles antibody protection in 6-month-old Malawian infants: Reconsider vaccination schedule?

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Abstract
Measles vaccination is currently recommended at 9 months, since maternal antibodies are supposed to protect infants until that age. In this study of 6-month-old Malawian infants 98.3% (58/59) had non-protective IgG levels against measles, irrespective of HIV exposure. Anticipating the first dose at 6 months could be considered.

KEYWORDS
infants, Malawi, maternal protection, measles, vaccination schedule

INTRODUCTION

In recent years, global resurgence of measles has been observed in all parts of the world, and disruptive measles outbreaks have been reported, mostly in the African and East Mediterranean regions [1] but also in high-income countries [2].

In Malawi, the measles vaccine was introduced in 1979, with the first dose recommended at 9 months of age; a second vaccine dose, at 15 months, was introduced in 2015 [3]. After the disruptive outbreak in 2010 [4], periodic mass campaigns have been implemented in addition to routine vaccination programmes [5]. Based on the Malawi Government's information, vaccine coverage was estimated at 90% in 2021 [6], but several studies reported a significant gap between official and field data [5, 7, 8].

Sustainable Development Goal: Good Health and Well-being

Infant protection against measles infection relies on placental transfer of maternal antibodies. Their early waning, observed by some authors [9, 10], could put infants at risk of severe complications and death from the disease in the case of infection [11]. Particular concern has been raised for the seroprotection status of infants belonging to vulnerable populations, such as HIV-exposed, uninfected (HEU) infants, for whom lower transplacental passage of maternal antibodies against pathogens has been demonstrated [12, 13].

The timing of measles vaccination (MV) is debated: WHO recommends delaying MV until maternal IgGs have waned because of more efficient vaccine response in the absence of maternal IgG [14]. By contrast, recent studies suggest that measles vaccine in the presence of maternal antibodies could have stronger non-specific beneficial effects on infant survival [15]. Field studies also support the idea that early MV may be important for improved measles control without hampering long-term immunity [16]. Some

countries characterised by a high HIV prevalence and recurrent measles outbreaks, such as South Africa, have already anticipated the first dose of measles vaccine at 6 months of age in an attempt to narrow the window of vulnerability to measles infection [17].

In Malawi, the last UNAIDS report estimates an HIV prevalence in the population of 7.7%, with an increasing number of HEU infants [18]. In the present study, we explored levels of measles IgG at 6 months, in two groups of HEU and HIV-unexposed uninfected (HUU) infants, to determine their seroprotection status against measles before the first dose of the vaccine.

MATERIALS AND METHODS

This study was conducted, from January 2019 to June 2021, within the structures of the Disease Relief through Excellent and Advanced Means (DREAM) Programme of the Community of S. Egidio, an Italian faith-based non-governmental organisation [19]. The study involved three clinical health centres that were all located in the Blantyre district: the urban centre in Mandala, and the peri-urban sites of Chileka and Machinjiri.

The present analysis is part of a larger study aiming to investigate the impact of maternal HIV infection and antiretroviral therapy (ART) on exposed infants under Option B+ (universal life-long ART for all HIV-positive women, independently of their disease stage) and assess the factors influencing maternal retention in care [20, 21]. Mothers living with HIV and HIV-negative mothers with their infants were enrolled between 32 and 36 weeks of gestation. Their HIV-positive (or negative) test was confirmed and demographic, clinical and socioeconomic information was collected. Mother/child pairs of both groups were followed with monthly visits until 12 months from delivery, and infant blood samples were collected at 6 months of age. The study aimed to enrol 150 women living with HIV and their infants and 150 HIV-negative women with their infants. But difficulties were encountered in enrolling HIV-negative women (a total number of 73 was reached), and a high rate of loss to follow-up (especially in HIV-negative women) occurred. Further, the study period partially overlapped the COVID pandemic which contributed to the lower-than-expected attendance to the follow-up visits (and the collection of blood samples). Therefore, only 59 blood samples from 6-month-old infants could be included in this study.

The measles IgG levels were evaluated using a commercial ELISA kit (Measles virus IgG ELISA) from IBL International GmbH (Hamburg, Germany). According to a previous study [22] and following the manufacturer's instructions, we considered values <150 mIU/mL not protective; values between 150 and 200 mIU/mL doubtful; and values >200 mIU/mL protective. Socio-demographic data were presented as medians with interquartile range or percentages. Geometric mean and 95% CI were used to summarise and analyse antibody levels. Differences between groups were evaluated using the χ^2 test or Fisher's exact test when appropriate for categorical variables and by the Mann–Whitney U test for quantitative variables. For all statistical analyses the SPSS software, version 27, was used (IBM, Somers, NY, USA).

Ethics

Ethical approval was obtained from the National Health Research Committee in Malawi (approval number 2085) and written informed consent was obtained from all women participating in the study and from all the parents and/or legal guardians of the infants included in the study.

RESULTS

The characteristics of the 59 infants (HEU = 45, HUU = 14) and of their mothers are reported in Table 1. Mothers with and without HIV had a similar median age, around 30 years ($p = 0.77$), and similar BMI values (HIV+: 24.8; HIV−: 26.3, $p = 0.97$, respectively). There were also no significant differences between the two groups in the socio-economic parameters (Table 1). The infant birth weight was 3.4 kg in both groups. All infants were breastfed until 6 months, and the median weight gain from 1 to 6 months of life was similar in the two groups (HEU: 3.0 kg, HUU: 2.8 kg, $p = 0.36$).

At 6 months seroprotective levels of measles IgG (≥200 mIU/mL) were observed only in one infant belonging to the HEU group. All the other infants had measles IgG <150 IU/mL. The measles IgG geometric mean was 82.1 mIU/mL (95% CI: 61.5–132.5) in the 45 HEU infants and 71.3 mIU/mL (95% CI: 64.6–80.3) in the 14 HUU infants ($p = 0.12$; Figure 1). There was no association between the measles IgG levels and the demographic and or socioeconomics indices (data not shown).

DISCUSSION

The results of this study suggest that most Malawian infants at 6 months of age, independent of their prenatal exposure to HIV, do not have protective levels of anti-measles IgG, and are susceptible to measles infection, well before the first dose of vaccine. In measles-endemic countries, the measles vaccine schedule recommends two doses at the age of 9 and 15 months, to avoid reduced immune response due to the presence of maternal antibodies. But at present, this timing is debated, since as shown in previous reports [9, 23] and as confirmed in the present study, at 6 months the maternal-derived measles antibodies can be well below the threshold considered adequate for protection. This leaves the infants vulnerable to the infection that in the first months of life is associated with severe complications and death [24]. Indeed,

TABLE 1 Infants and maternal characteristics.

	HEU infants	HUU infants	*p* Value
Number of infants	45	14	
Sex ratio (M/F) %	64.4/35.6	35.7/64.3	0.11
Weight at birth (kg)	3.4 (3.1–4.0)	3.4 (2.7–3.7)	0.36
Weight gain 1–6 months (kg)	3.0 (2.4–3.4)	2.8 (2.4–3.7)	0.89
Maternal age (years)	29.5 (23.0–33.7)	30.0 (25.5–32.5)	0.77
Maternal BMI	24.8 (22.5–29.8)	26.3 (22.5–28.8)	0.97
ART duration of HIV+ mothers at enrolment (months)	8.8 (4.5–90.2)	-	-
Maternal antiretroviral regimen		-	-
TDF/3TC/EFV	41 (91.1)		
TDF/3TC/DTG	4 (8.9)		
Residency (*n*, %)			0.26
Urban	11 (24.4)	1 (7.1)	
Semirural/rural	34 (75.6)	13 (92.9)	
Water at home (*n*, %)	26 (57.8)	10 (71.4)	0.53
Electricity at home (*n*, %)	18 (38.6)	5 (35.7)	0.84
Education (*n*, %)			0.76
Primary or no education	25 (55.6)	9 (64.3)	
Secondary or higher	20 (44.4)	5 (35.7)	
Number of children at home (*n*, %)			0.11
None	6 (13.3)	0	
1	9 (20.0)	2 (14.3)	
2 or more	30 (66.7)	12 (85.7)	

Note: Values are expressed as medians and (IQR) and percentage.
Abbreviations: 3TC, lamivudine; DTG, dolutegravir; EFV, efavirenz; TDF, tenofovir.

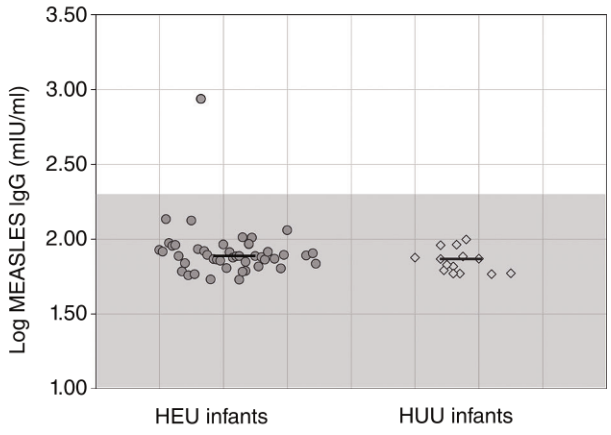

FIGURE 1 Anti measles IgG in 6-month-old infants born from women living with HIV (HEU) and from HIV negative women (HUU). The black bars represent the geometric means of the two groups and the grey shadow indicates the area below protective levels (≥200 mIU/mL).

WHO reported that 12% of all cases of measles in the world involved infants too young to be vaccinated [25].

It is important to note that the insufficiency in measles IgG levels was not specific for HEU infants and did not seem a direct consequence of an impaired transplacental passage and/or of an early waning of maternal antibodies due to maternal HIV since levels were similar in HEU and HUU infants. These data are consistent with very recent serosurveillance studies reporting a high proportion of 3–6-month-old infants susceptible to measles in South Africa [17], in China [26], in India [27] and in high-income European and American countries [2, 23, 27].

In this study, the measles IgG levels were particularly low; even considering the protection threshold of 150 mIU/mL, only one infant had levels well above the limit (863.1 mIU/mL), suggestive of measles exposure rather than maternal IgG passive transfer. Similar results were obtained in a previous study in Burkina Faso and Guinea-Bissau, where nearly all 4–7 month-old children were susceptible to measles infection well before the currently recommended age for MV [28].

The schedule for MV was designed in settings of frequent natural infection and early exposure to measles. It has been demonstrated that naturally infected mothers transfer a higher amount of measles antibodies to their infants compared to vaccinated mothers [23]. In our study, 53/59 (89.8%) of the mothers were born after the introduction of the infant MV in Malawi. Thus, vaccinated mothers may transfer fewer maternal measles IgG in these children, leaving them more susceptible to the infection until the first dose of the vaccine.

The current measles vaccine policy seeks to optimise seroconversion rates since an early vaccination can lead to blunted antibody responses and lower IgG levels later in life; however, evidence from randomised studies in low-income countries [29–32] suggests that an earlier MV, in the presence of maternal antibodies, could reduce all-cause mortality, both providing infant protection from measles infection and conferring beneficial non-specific effects against non-measles infections. In light of these results, the vaccine strategy could be reconsidered, but at present, only a few countries, including South Africa, have anticipated to 6 months of age the MV [17].

Despite the small sample size, which represents the major limitation of this study, we believe that our data can be used as an indicator that larger studies are needed to confirm the low prevalence of protective antibodies in infants in Malawi, a country where measles outbreaks frequently occurred and HIV infection prevalence is high [4, 18]. Our results, if confirmed, suggest that a change in the MV schedule could be taken into consideration to enhance infant protection.

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