

Short communication

The association between age and the development of respiratory syncytial virus neutralising antibody responses following natural infection in infants

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ABSTRACT

To determine the age at which infants mount significant neutralising antibody responses to both natural RSV infection and live vaccines that mimic natural infection, RSV-specific neutralising antibodies in the acute and convalescent phase sera of infants with RSV infection were assayed. Age-specific incidence estimates for hospitalisation with severe RSV disease were determined and compared to age-specific neutralising antibody response patterns. Disease incidence peaked at between 2 and 3.9 months of life. Following natural infection, relative to the mean acute phase antibody titre, the mean convalescent titre was lower in the 0–1.9 month age class, no different in the 2–3.9 month age class and greater in all age classes greater than 4 months. These data suggest effective vaccination with live vaccines that mimic natural infection may not be achieved before the age of 4 months. Maternal vaccination may be an alternative to direct infant vaccination in order to protect very young babies.

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1. Introduction

RSV is an important cause of acute lower respiratory infection in infants and elderly adults [1]. Recent estimates have shown the considerable global burden of RSV-associated disease [2] and have highlighted the need for the development of effective vaccines for use in vulnerable populations. Severe RSV infection in infants can result in the development of potentially life-threatening severe pneumonia [3] and is increasingly being recognised as predisposing to severe pneumonia in the short term [4] and as a risk factor for the development of wheeze and asthma in later life [5]. Previous studies have provided evidence that immunity from lower respiratory tract disease correlates with levels of neutralising antibodies [6,7], an assertion that is supported by the clinical experience with the prophylactic neutralising monoclonal antibody, Palivizumab,

which has been associated with up to a 78% reduced risk of hospitalisation among premature infants [8].

The key target group for vaccination against RSV is infants under the age of 6 months in whom the risk of severe disease is greatest. The prospect of active immunisation of this population is hindered by safety concerns related to the administration of non-replicating vaccines which are associated with potentiation of disease upon re-exposure in both infants [9] and animals [10]. In contrast, replicating vaccines such as live-attenuated vaccines have been shown in several clinical trials to have a relatively good safety profile [11,12] and are thought to be the safest alternative for providing direct protection for infants. RSV vaccine development faces the additional challenge of vaccinating infants at an age that is associated with both a high prevalence of maternally derived antibodies as well as relative immunological immaturity. The association between age and the neutralising response to natural RSV infection in infants is therefore an important consideration in the development of live-attenuated vaccines, whose antigenic profile is thought to closely mirror that of wild type virus and which might therefore be expected to induce responses that broadly resemble natural infection responses. This study investigated the development of neutralising antibody responses generated upon natural infection in early infancy. The implications of the results on infant vaccination strategy are discussed.

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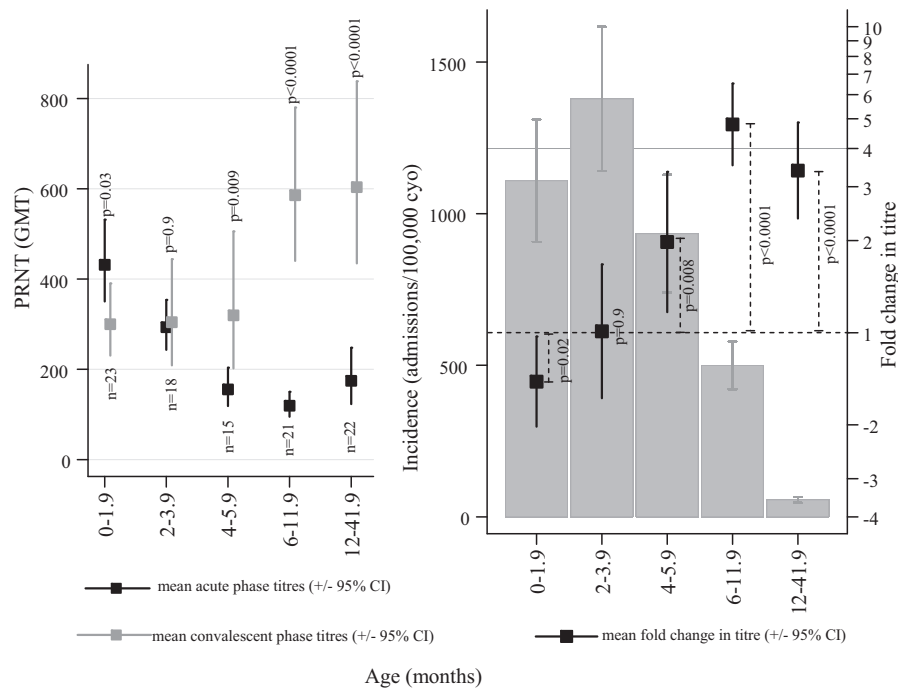


Fig. 1. (a) The relationship between acute and convalescent phase titres with age. Mean acute phase titres are depicted by the black filled boxes (with corresponding 95% confidence intervals) while mean convalescent phase titres are shown in grey filled boxes (with 95% confidence intervals). The *p* values above each mean acute/convalescent pair indicate whether the mean differences in titre are statistically significant. The values below the acute/convalescent pair are the number of individuals in each age class whose acute/convalescent responses were analysed. (b) Comparison between age-specific incidence estimates of admission with severe disease and the ability to generate a neutralising antibody response following natural infection. The incidence of admission with RSV associated pneumonia within the Kilifi Health and Demographic Surveillance System (with corresponding 95% confidence intervals) is shown in the grey bars while the mean fold change in neutralising antibody titre from the acute to convalescent phases of infection are depicted using the black filled boxes (with corresponding 95% confidence intervals). The horizontal dashed line indicates a 1-fold change in titre; above which a rise in titre is observed and below which a decline in titre is observed. The solid horizontal line indicates the 4-fold level that is used to define a seroconversion. The *p* values against the vertical dashed lines connecting the mean fold changes in titre to the horizontal dashed line indicating a 1-fold change in titre indicate whether the age-specific mean fold changes in titre are significantly different from 1. The association between age-specific incidence estimates of disease and fold changes in titre from the acute to convalescent phases of infection is not causal.

2. Materials and methods

The study was set in the Kilifi District Hospital (KDH) on the coast of Kenya [14]. Acute and convalescent phase sera, collected at admission and approximately 4 weeks after admission, respectively, were obtained from 99 patients aged 6 days to 41 months who were admitted to KDH with severe RSV infection. RSV diagnosis was done using an immunofluorescent antibody test on nasopharyngeal samples [13]. Neutralising antibodies to the A2 strain of RSV were measured by a previously described microplaque reduction neutralisation assay [15]. Written informed consent was sought from children's parents while ethical approval for the study was granted by the Kenya Medical Research Institute Ethical Review Committee.

Data were analysed using Stata (StataCorp, Texas). For the estimation of both disease incidence and antibody response, data were stratified in five age classes: 0–1.9, 2–3.9, 4–5.9, 6–11.9 and 12–41.9 months of age. Age-specific incidence estimates for admission with severe RSV pneumonia were calculated for the period January 1st 2002 to December 31st 2008, by dividing the number of pneumonia admissions resident in KHDSS with a laboratory diagnosis of RSV by the resident population size at the midpoint of the study period [13]. The difference between the mean acute and convalescent phase titres in different age classes was tested using a paired *t* test. To determine whether a significant response to infection was generated following infection, the magnitude of the neutralising antibody response – expressed as fold change in titre from the acute to convalescent phases of infection – was compared to a value of 1 using an unpaired *t* test.

3. Results

In the first year of life there was a progressive decline in the titre of acute phase neutralising antibodies, which coincided with an increase in convalescent titres over the same period (Fig. 1a). The incidence of severe RSV associated pneumonia during the study period rose sharply after birth; starting at 1108 admissions/100,000 child years of observation (cyo) at between 0 and 1.9 months of age (95% CI: 906–1310) and peaking at 1378 admission/100,000 cyo (95% CI: 1140–1616) at between 2 and 3.9 months of age. The incidence of severe RSV pneumonia thereafter declined to 934 admissions/100,000 cyo (95% CI: 740–1128) in the 4–5.9 month age class, and was lowest in the 6–11.9 and 12–41.9 month age classes at 499 admissions/100,000 cyo (95% CI: 420–578) and 56 admissions/100,000 cyo (95% CI: 46–65), respectively, as shown in Fig. 1b. In the first year of life the response to infection, measured as fold change in neutralising antibody titre from the acute to convalescent phases of infection, increased progressively with age. In the first 2 months of life (0–1.9 months), there was a significant decline in the neutralising response, i.e., fold change less than unity (*p* = 0.02; Fig. 1), while no significant change in titre was observed at 2–3.9 months of age (*p* = 0.1). However, as shown in Fig. 1b, in all age classes of children older than 4 months of age, there was a significant rise in the titre of neutralising antibodies following natural infection.

The proportion of infants who had a detectable rise in titre from the acute to convalescent phases of infection (fold change in titre >1) increased with age as shown in Fig. 2. In the youngest age class (0–1.9 months old), only 26% of infants with a confirmed RSV

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