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Post-immunization leucocytosis and its implications for the management of febrile infants

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ABSTRACT

Aims: Clinical guidelines for management of infants with fever but no evident focus of infection recommend that those aged 1–3 months with a white cell count >15 × 10^9/l have a full septic screen and be admitted for parenteral antibiotics. However, there is limited information about leucocyte changes following routine immunization, a common cause of fever. We investigated white cell counts shortly after routine immunization in Ugandan infants under 3 months of age.

Methods: White cell counts were measured in 212 healthy infants following routine immunizations (DTwP-HepB-Hib, oral polio and pneumococcal conjugate 7 vaccines) received prior to 3 months of age.

Results: Mean leucocyte counts increased from 9.03 × 10^9/l (95% confidence interval 8.59–9.47 × 10^9/l) pre-immunizations to 16.46 × 10^9/l (15.4–17.52 × 10^9/l) at one-day post-immunizations at 6 weeks of age, and 15.21 × 10^9/l (14.07–16.36 × 10^9/l) at one-day post-immunizations at 10 weeks of age. The leucocytosis was primarily a neutrophilia, with neutrophil percentages one-day post-immunization of 49% at 6 weeks of age and 46% at 10 weeks of age. White cell parameters returned to baseline by two-days post-immunization. No participant received antibiotics when presenting with isolated fever post-immunization and all remained well at follow-up.

Conclusions: In our study almost half the children <3 months old presenting with fever but no evident focus of infection at one-day post-immunization met commonly used criteria for full septic screen and admission for parenteral antibiotics, despite having no serious bacterial infection. These findings add to the growing body of literature that questions the utility of white blood cell measurement in identification of young infants at risk of serious bacterial infections, particularly in the context of recent immunizations, and suggest that further exploration of the effect of different immunization regimes on white cell counts is needed.

This observational work was nested within a clinical trial, registration number ISRCTN59683017.

1. Introduction

Fever is one of the most common reasons for presentation of children to medical professionals [1]. Children presenting with no obvious focus for their infection can pose a diagnostic challenge to clinicians. Algorithms exist to assist in the identification of children who would benefit from investigation and admission to hospital for treatment. These guidelines are particularly stringent for febrile infants less than 3 months old, due to the increased risk of occult serious bacterial infections [2]. Guidelines used in the UK [3], and in adapted forms worldwide, advise that a full blood count and partial septic screen should be performed on any infant presenting with a fever >38 °C without focus when less than 3 months of age, even if otherwise well-looking and regardless of recent immunization history. Infants who have a white cell count of >15 × 10^9/l are then admitted to hospital for a full septic screen, including lumbar puncture, and parenteral antibiotics whilst culture results are pending (usually a minimum of 48 h).

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Infants worldwide commonly receive a number of vaccinations in the first few months of life, generally with multiple antigens administered on one day [4]. These vaccines are highly immunostimulatory and the occurrence of fever >38 °C following routine vaccinations is well recognised. However, the effect on white cell counts of the co-administration of multiple vaccine antigens, such as those received during primary immunizations, is unknown. Studies conducted in the 1980s in Finland and the USA in a small number of older infants, showed an increase in white cell counts post administration of the combined Diptheria-Tetanus-whole cell Pertussis (DTwP) vaccination [5]. However, few similar studies have been published looking at younger infants and using the enhanced combination of vaccine antigens currently in use.

Lack of knowledge regarding alterations to white cell count levels following routine immunization could severely impede clinical decision making during the assessment of a feverish child. This may have negative consequences for the child due to unnecessary invasive investigations and antibiotic administration. This study investigated alterations to white cell counts during the period immediately following routine immunization, in the first 3 months of life.

2. Methods

Post-immunization blood samples were collected from 212 Ugandan infants as part of a randomised controlled trial investigating the impact of BCG vaccination on the innate immune system (described elsewhere [6]). In brief, infants were randomised to receive BCG either at birth or at 6 weeks of age. All other routine immunizations were given as per Ugandan national guidelines: oral polio vaccine (OPV) at birth and pentavalent vaccine (diptheria-tetanus-whole-cell pertussis/*Haemophilus influenzae* B/Hepatitis B), OPV and pneumococcal vaccine (PCV10) at 6 weeks, 10 weeks and 14 weeks of age (hereafter referred to as 'primary immunization'). Infants were then randomly assigned to have venous blood samples taken on two out of four possible time points: (1) 5 days of age, (2) 6 weeks of age, 1 day following immunization, (3) 6 weeks of age, 5 days following routine immunization and (4) 10 weeks of age, 1 day following routine immunization. In practice, blood samples were taken at a range of times post-routine immunization, due to delayed attendance at clinic for some participants. Infants with blood samples taken more than 15 days following immunization were excluded from analysis (n = 1). BCG vaccination in the delayed group was given after blood sample 2 but prior to blood sample 3. However, upon analysis, no significant impact of the different BCG schedules on white blood cell count was shown and data were analysed together.

Anthropometry, vital sign measurement and clinician review of participants occurred at each appointment. Temperatures were measured using a digital axillary thermometer, following current best practice recommendations. Active follow-up of participants occurred for the duration of the trial with open access to clinician review and treatment, as well as weekly telephone follow-up, to confirm health status.

Full blood counts were obtained using the automated Coulter AcT 5diff CP (Beckman-Coulter, California, USA), from 0.5 ml of venous blood drawn from the dorsum of the hands or feet into an EDTA containing microtainer (Becton-Dickson).

Data were analysed using STATA version 14.1 (StataCorp, Texas, USA) and graphs produced using Prism 6 (GraphPad Software, Inc. California, USA). Results were normally distributed so means with 95% confidence intervals are reported, with Student's *t*-test used for comparison of means pre- and post-immunization. Changes in mean values over time were analysed using a random effects model to account for repeated measurements and including both linear and quadratic terms for time to allow for a non-linear relationship.

Ethical approval for the trial was obtained from the Uganda Virus Research Institute Research and Ethics Committee (Ref: GC/127/13/11/432), the Uganda National Council for Science and Technology (Ref: HS 1524), The Office of the President of Uganda and the London School of Hygiene & Tropical Medicine (Ref: 6545). The study was conducted according to the principles of the Declaration of Helsinki. Written, informed consent of mothers was obtained by trained study nurses prior to any procedures.

3. Results

Two hundred and twelve infants provided blood samples for this study, 49% of them male. The background of the population was East African, primarily of the Buganda tribe and participants came from a mixture of urban, semi-urban and rural fishing communities. No participant was severely malnourished at the time of blood sample collection.

Average white cell counts were significantly increased at one-day post receipt of primary immunizations at both 6 weeks of age (16.46×10^9/l (95% confidence interval 15.40–17.52 $\times 10^9$/l) and 10 weeks of age (15.21×10^9/l (14.07–16.36 $\times 10^9$/l)), compared to pre-immunization values (9.03×10^9/l (8.59–9.47 $\times 10^9$/l), p-values for difference with post-immunization levels <0.0001, see Table 1 and Fig. 1).

This rise in mean total leucocytes was short-lived, returning to levels not significantly different from baseline by two days post-immunization, but continuing to decline up to six-days post-immunization ($p < 0.0001$) (Fig. 2). Although mean white cell counts at one day post-immunization fell within the normal range expected for age (5.0–19.5 $\times 10^9$/l) [7], there was a wide range of values (8.00–32.90 $\times 10^9$/l at one-day post 6-week immunization and 6.20–29.80 $\times 10^9$/l at one day post 10-week immunization). At both time-points an average of 22% of white cell counts measured fell outside of the normal range for age. At one day post-immunization, on average 53% of measured white cell counts were above the 15 $\times 10^9$/l cut-off for further intervention when managing a febrile child <3 months old (Fig. 1).

The leucocytosis observed at one-day post immunization was primarily a neutrophilia (Table 1 and Fig. 3). Little change occurred to total lymphocyte levels, other than an expected increase with age (see Fig. 3). As a result at one-day post-primary immunization, the percentage of the white cell count made up by lymphocytes dropped as the percentage accounted for by neutrophils increased (Table 1 and Fig. 3). The average percentage of neutrophils was above the normal range for age (up to 32% neutrophils [7]) at one-day post-primary immunization at both 6 weeks of age (49%) and 10 weeks of age (46%). Total monocyte and basophil levels mimicked changes to neutrophils post-immunization, though to a much smaller extent (Table 1). The reverse occurred with eosinophils, with total eosinophils dropping at 1-day post-immunization and rising by day 2. The changes to monocyte, basophil and eosinophil count were only significant at the 6-week time-point. There was little change to the percentage of monocytes, eosinophils and basophils by immunization status.

Linear regression analysis provided good evidence ($p < 0.0001$) of a weak, positive association of temperature and white cell counts, with each one degree Celsius increase in temperature associated with a 0.04 $\times 10^9$/l increase in white cell count (Fig. 4). Of all children studied that presented with a fever >38 °C when the blood sample was taken, 5 out of 11 (45%) had a white cell count above the currently recommended threshold for further investigation and inpatient management with IV antibiotics. A further 17 mothers reported that their children had been pyrexial prior to presentation. Of these, 3 (18%) had white cell counts above 15 $\times 10^9$/l. All