The Effects of Strain Variation on Respiratory Syncytial Virus infection and Immunity

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Introduction

- RSV re-infacts throughout life despite the development of an effective but transient neutralising antibody response.
- Neutralising antibodies are directed at two variable surface expressed glycoproteins, G and F.
- RSV epidemiology is characterized by:
  - Cyclical alterations in dominance between its two main antigenic groups, A and B.
  - Emergence and extinction of within-group strains & periodically global dominance of recently emergent strains (eg a recent 20amino acid duplication in the G2 protein of RSV B variants that has attained global dominance).
  - Antigenic drift within attachment and Fusion proteins
- This suggests that:
  - There are underlying mechanisms through which temporal selection pressures confer a transmission advantage to one group relative to the other at a particular point in time (White et al, O5).
  - Decline & extinction of strains is driven by immune pressure
  - Antigenic drift might be driven by immune response
- We hypothesized:
  - At the population level, immunity to primary infections will be strongly group specific.
  - Responses to contemporary infections will be poorly cross reactive against older strains.
- We investigated group & strain specific antibody responses following RSV infections in children aged 0 to 47 months during RSV epidemics of 2006, 2007 (dominated by RSV A) and 2003,2008 (dominated by RSV B) in Kilifi District Hospital (KDH), a rural hospital on the Kenyan coast.

Methods

Sample set
- A nasal specimen and acute blood were collected from children admitted to KDH with WHO defined severe or very severe pneumonia. Samples were screened for RSV Ag by immunofluorescent antibody test. Convalescent blood was collected from RSV positives.

Plaque Reduction & Microneutralisation Assay
- Neutralising titres were determined using the Plaque Reduction and Neutralisation Assay as previously described (Coates,1966).
- We adopted the ELLISPOT reader to count plaques which significantly increased throughout without sacrificing accuracy.
- Neutralising titres were calculated using the Spearman-Karber method (Cohen et al, 2007). Results are expressed as neutralising dose 50, ND50 (+/- 95% CL).

Objectives

1. Quantify homologous and heterologous group neutralising antibody responses following primary and subsequent infection and estimate cross neutralisation titres
2. Determine cross reactivity between RSV A/B strains from the 2000s with RSV A/B strains from the 1960s.
3. Determine the serological effect of the recent 20 amino acid duplication

Results

Neutralising Antibody Responses in the Convalescent Phase

- The magnitude of the neutralising response increases with age. Convalescent titres are significantly higher when the group identity of the test and infecting strain are matched.
- The magnitude of the response did not vary despite the temporal distances between test and infecting strains.

Discussion

- We found evidence that RSV antibodies are strongly group specific and are poorly cross reactive.
  - Supports hypothesis of immune mediated group replacement
  - Suggests future vaccines based on one strain may alter RSV epidemiology.
- Despite over 40 years of antigenic drift, no significant loss of serological recognition was evident.
  - Suggests antigenic drift is not a mechanism for immune escape
  - Future vaccines may not need periodic updates.
- The 20 amino acid duplication did not result in loss of serological recognition

Ongoing work

- Measurement of RSV A and B neutralising antibodies in a cohort of infants recruited at birth and followed up for 2 years of age
- The relative magnitude of RSV A and B specific antibodies at all time points within during follow up will be tested
- The relative duration of group specific immunity following an antigen confirmed infection
- Some preliminary data for RSV A antibodies only are shown on the right

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