Neisseria lactamica induces anti-Neisseria meningitidis B-cell responses

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Background:

• There is an inverse relationship between pharyngeal colonisation with *Neisseria lactamica* (Nlac) and *Neisseria meningitidis* (Nmen).

• Controlled human infection with Nlac displaces Nmen and prevents new Nmen colonisation events.

• The mechanism underlying this phenomenon is not yet elucidated. If it was understood, it could be exploited to develop novel strategies to prevent Nmen colonisation +/- disease.

• Nlac colonisation does not induce anti-Nmen serum bactericidal activity (SBA).

• We propose that the induction of cross-reactive adaptive cellular or humoral responses, independent of SBA, may be responsible for observed effect.

Aims:

• To assess whether Nlac colonisation induces anti-Nmen B cell responses.

• To assess whether B cell response frequencies were associated with Nlac colonisation density.
Study design:

- Healthy adults randomised 2:1 to received intra-nasal inoculation with intervention (Nlac, $10^5$ CFU) or control (PBS).

- Nlac/Nmen colonisation status assessed at 0, 7, 14 and 28 days (culture of oropharyngeal swab and nasal wash).

- Blood taken at all time points to assess cellular responses.

Study flow diagram:

**Screening**
- Assessed for eligibility (n=50)
  - Ineligible (n=18)
    - N. meningitidis colonised (n=5)
    - N. lactamica colonised (n=2)
    - Hb below cut off (n=8)
    - Other reason (n=2)

**Eligible (n=32)**
- Withdrawn prior to allocation (n=1)
  - New immunocompromised contact (n=1)

**Allocation**
- Allocated to intervention (n=20)
- Allocated to control (n=11)

**Follow-up visits (days 7, 14 & 28 post-inoculation)**

**Immunological analysis**
- Excluded from immunological analysis (n=2)
  - N. meningitidis colonisation at day 0 (n=1)
  - Not colonised with N. lactamica following inoculation (n=2)
- Excluded from immunological analysis (n=1)
  - N. meningitidis colonisation at day 0 (n=1)
- Analysed (n=17)
- Analysed (n=10)

**Nlac/Nmen colonisation:**
- Nlac colonised (blue)
- Nmen colonised (red)
- TS (oropharyngeal swab)
- NW (nasal wash)

**Key:**
- Nlac colonised (blue)
- Nmen colonised (red)
- TS (oropharyngeal swab)
- NW (nasal wash)
Colonisation with Nlac induces anti-Nmen $B_{PLAS}$ & $B_{MEM}$ responses

IgA/IgG $B_{PLAS}$ ELISpot

Collated $B_{PLAS}$ data

Collated $B_{MEM}$ data

IgG $B_{MEM}$ ELISpot

**Key:**
- Keyhole limpet haemocyanin (Klh)
- Nlac (Y92-1009) dOMV (Nlac)
- Nmen (H44/76) dOMV (Nmen)
- Influenza haemagglutinin (H1N1) (Flu)
Nlac-specific $B_{\text{PLAS}}$ responses and IgG titers are associated with Nlac colonisation density

Nlac colonisation density vs. IgA $B_{\text{PLAS}}$ responses

Nlac colonisation density vs. day-28 IgG responses (plasma)

Nlac colonisation density vs. baseline Nlac/Nmen IgG $B_{\text{MEM}}$ responses

Correlations assessed with Spearman’s Rho ($r_s$) (*$P < 0.05$)
Conclusions

- Colonisation with Nlac induced $B_{PLAS}$ and $B_{MEM}$ responses specific to Nlac and Nmen, suggesting that the previously observed protective effect of Nlac on Nmen may have an immunological basis.

- Nlac colonisation density negatively correlated with anti-Nlac IgG titers and anti-Nlac IgA-secreting $B_{PLAS}$ frequencies suggesting that the magnitude of these responses may play a role in controlling Nlac colonisation density.

- We predict that protection against Nmen colonisation may only occur in those where Nlac colonisation results in the formation of anti-Nmen B cell and antibody responses.

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