\textbf{Neisseria lactamica induces anti-Neisseria meningitidis B cell responses}

Adam P. Dale\textsuperscript{1}, Anastasia A. Theodosiou\textsuperscript{1}, Jay R. Laver\textsuperscript{1}, Eleanor F. Roche\textsuperscript{1}, Alison R. Hill\textsuperscript{1}, Andrew Gorringe\textsuperscript{2}, Marta E. Polak\textsuperscript{1}, Andrew T. Vaughan\textsuperscript{1}, Robert C. Read\textsuperscript{1}.

1. Academic Unit of Clinical and Experimental Sciences, University of Southampton, Southampton, SO16 7YD, UK.
2. Public Health England, Porton Down, Salisbury, SP4 0UG, UK, correspondence to: e.p.dale@solent.ac.uk

\textbf{Introduction & Aims}

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Coloinisation with Neisseria lactamica (Nlac) prevents Neisseria meningitidis (Nmen) colonisation and disease. If the mechanism underlying this effect was elucidated it could be exploited to develop novel strategies to protect against Nmen colonisation and disease. We theorised that an admixture of bacterial components independent of SBA may be implicated in this protection and performed a Nlac controlled human infection experiment to test this hypothesis.

\textbf{Aims}

1. To establish if pharyngeal colonisation with Nlac induces Nlac-specific B cell responses that are cross-reactive with Nmen.
2. To ascertain whether the magnitude of Nlac-specific B cell responses induced following Nlac colonisation were associated with Nlac colonisation density.

\textbf{Methods}

\begin{itemize}
\item 31 participants were randomised to receive intra-nasal inoculation with \(10^3\) colony-forming units (CFU) of Nlac (Y92-1009) suspended in 1ml phosphate buffered saline (PBS) (intervention), or 1ml PBS (control).
\item Nlac and Nmen colonisation status was assessed at baseline and at 7-, 14- and 28-days post-inoculation by culture of oropharyngeal swabs and nasal wash. Nmen colonisation density was measured in nasal wash.
\item Nlac (Y92-1009)-specific and Nmen (H44/76)-specific IgG-secreting and IgG-secreting plasma cell (BPLAS) and IgG memory B cell (BMEM) frequencies were quantified in blood at baseline and post-inoculation time points using enzyme-linked immunosorbent assays (ELISPOT).
\item Nlac-specific and Nmen-specific IgG tiers were measured in plasma using enzyme-linked immunosorbent assays (ELISA).
\end{itemize}

\textbf{Results}

\begin{enumerate}
\item Colonisation with Nlac induces anti-Nlac and anti-Nmen B\textsubscript{PLAS} and B\textsubscript{EM} responses. PBMCs were derived from Nlac-colonised and PBS-inoculated participants and assessed by ELISPOT for the presence of IgG-secreting (A-D) and IgG-secreting (E-H) B\textsubscript{PLAS} and IgG B\textsubscript{EM} (FLU) specific for Nlac Y92-1009-dOMV (A, C, E, G, I, K) and Nmen H44/76-dOMV (B, D, F, H, J, L). B\textsubscript{PLAS} and B\textsubscript{EM} were visualised as SFU, having adjusted for non-antigen-specific SFU by subtraction of SFU enumerated in KLH-coated wells. For B\textsubscript{EM} data, the highest number of SFU per 2 x 10\(^5\) PBMCs was chosen (day 7-28) for both anti-antigen baseline. Bars indicate median. *P \leq 0.05, **P \leq 0.01, ***P \leq 0.0001 by Wilcoxon matched-pairs signed rank test (n = 17 Nlac-colonised participants, n = 10 PBS-inoculated participants).
\item Anti-Nlac IgA titer between days 0 and 28 amongst participants with (+) and without (-) detectable IgG B\textsubscript{EM} responses was induced (Figure 3) where anti-Nmen IgG-secreting BPLAS responses were induced.
\item The observation that anti-Nlac IgG titer and anti-Nmen IgG-specific B\textsubscript{EM} frequencies amongst volunteers with (+) and without (-) detectable IgG B\textsubscript{EM} responses to both Nlac (right-handed circles) and Nmen (left-handed circles) at baseline. (E-F) Nmen- and Nlac-specific IgG B\textsubscript{EM} frequencies amongst volunteers with (+) and without (-) detectable anti-Nmen IgG-secreting B\textsubscript{PLAS} responses, comparing day 0 and day 28 frequencies with the lowest frequency measured on either day 7 or day 14. (G-H) Increase in anti-Nmen and anti-Nlac IgG titre between days 0 and 28 amongst participants with (+) and without (-) a detectable anti-Nmen IgG-secreting B\textsubscript{PLAS} response. *P \leq 0.05, **P \leq 0.01, ***P \leq 0.0001 by Mann-Whitney test and Kuusala-Wallis test with Dunn’s multiple comparisons test.
\item Colonisation with Nlac induces IgG-secreting and IgG-secreting B\textsubscript{PLAS} and B\textsubscript{EM} with specificity to Nlac and Nmen (Figure 3).
\item That Nmen-specific IgG B\textsubscript{EM} frequencies were higher amongst Nlac colonised participants where Nlac-specific and Nmen-specific IgG B\textsubscript{EM} were both detectable at baseline (Figure 4A) suggests that Nlac colonisation may have boosted pre-existing cross-reactive B\textsubscript{EM} responses. This theory is further supported by the observation that Nmen-specific IgG B\textsubscript{EM} frequencies reduced amongst Nlac-colonised participants where anti-Nmen IgG-secreting B\textsubscript{PLAS} responses were induced (Figure 4E).
\item If the observation of anti-Nmen B\textsubscript{PLAS} or antibody induced by Nlac colonisation is responsible for the protective effect afforded by Nlac on Nmen then we would predict protection would only be afforded in those where anti-Nmen responses were induced. We intend to test this hypothesis using the Nlac controlled human infection model.
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\textbf{Conclusions & Future Work}

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\textbf{Acknowledgements}

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