**BACKGROUND AND AIMS**

Colonization of the upper respiratory tract with *Streptococcus pneumoniae* (Spn) is the precursor of pneumococcal pneumonia and invasive disease. Following exposure, however, it is unclear which human immune mechanisms determine whether a pathogen will become a colonizer or be eradicated.

We used a human challenge model to investigate host-pathogen interactions in the first hours and days following intranasal exposure to Spn. Using a novel home sampling method, we measured early immune responses after intranasal pneumococcal exposure, and the dynamics of bacterial density in the nose and saliva.

**METHODS**

40 healthy adults aged 18-32 were intra-nasally inoculated with live 6B Spn (80,000 CFU in 100ul saline per nostril).

Volunteers were provided with a bag containing sample collection tubes, freezer packs and a USB temperature logger. They self-collected saliva and nasosorption at specific times after Spn exposure. Samples were store in fridge/freezer and storage temperature plus collection times were recorded.

We used 6A/B specific qPCR assays to measure Spn in saliva and nasal lining fluid as well as 30-plex Luminex to measure immune responses. The analysis was repeated and evaluated with a separate cohort of 23 volunteers aged 19-49 years.

**RESULTS**

Culture-positives and saliva clearers showed a significant induction of multiple cytokines at 24hrs post exposure.

Nasal clearers had limited cytokine induction at any time point measured during the first 48hrs, with only two cytokines significantly induced at 24hrs post exposure.

The data highlight that multiple mechanisms of protection must be considered when establishing correlates of protection against bacterial colonisation such as speed of clearance, local phagocytic function and acute mucosal inflammatory responses to inform design and testing of novel vaccine candidates.

**CONCLUSIONS**

- Nasal colonization can take up to 24hrs to become established
- Culture-positives: No early Spn in saliva, low induction of cytokines compared to baseline and lack of neutrophil responses during the first hours and days post exposure
- Two distinct bacterial clearance profiles are associated with protection against colonization

**Saliva Profiles**

Distinct Spn kinetics between culture-positives and culture-negatives

**Nasal Profiles**

Spn migrated posteriorly or attached/internalised to nasal epithelium within 24 hrs post exposure

**Immune Profiles**

Culture-positives

Nasal clearers had limited cytokine induction at any time point measured during the first 48hrs, with only two cytokines significantly induced at 24hrs post exposure.

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- Two distinct bacterial clearance profiles are associated with protection against colonization

**Saliva clearers:** Early Spn detection in saliva at 1hr post exposure followed by a significant induction of an inflammatory response and increased neutrophil activity 24hrs post exposure

**Nasal clearers:** No early Spn detection in saliva, immediate clearance of bacteria in the nose by the activity of pre-existent mucosal neutrophils

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