Introduction and objectives Randomised controlled trials of vitamin D to prevent acute respiratory infection have yielded mixed results. We conducted an individual patient data (IPD) meta-analysis to identify factors that may explain this heterogeneity.
Methods We performed an IPD meta-analysis of 25 trials of vitamin D supplementation with incidence of acute respiratory infection as a pre-specified outcome (total 11,321 participants, aged 0 to 95 years). We used one-step logistic regression with random effects adjusting for age, sex, study duration and clustering by study. Pre-specified sub-group analyses were done to determine whether effects of vitamin D on risk of acute respiratory infection varied according to baseline 25-hydroxyvitamin D (25[OH] D) concentration or dosing regimen.
Results IPD were obtained for 10,933/11,321 (96.6%) participants. Vitamin D supplementation reduced risk of acute respiratory infection among all participants (adjusted Odds Ratio [aOR] 0.88, 95% CI: 0.81 to 0.96, P = 0.003; P for heterogeneity < 0.001). Sub-group analysis revealed a strong protective effect among individuals with baseline 25(OH) D < 25 nmol/L (aOR 0.62, 95% CI: 0.45 to 0.83, P = 0.002), not seen among those with higher levels (aOR 0.91, 95% CI: 0.78 to 1.05; Pinteraction = 0.01). A protective effect was also seen in individuals receiving daily or weekly vitamin D without additional bolus doses (aOR 0.81, 95% CI: 0.72 to 0.91, P < 0.001), but not in those receiving one or more bolus doses (aOR 0.97, 95% CI: 0.86 to 1.10, Pinteraction = 0.05). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (aOR 0.98, 95% CI: 0.80 to 1.20, P = 0.83). The body of evidence contributing to these analyses was assessed as being of high quality.
Conclusions Vitamin D supplementation was safe, and it protected against acute respiratory infection overall. Very deficient individuals and those not receiving bolus doses experienced the most benefit.

S103 NON-TYPEABLE HAEMOPHILUS INFLUENZAE DOWNREGULATES RELEASE OF BETA-DEFENSIN-1 FROM BRONCHIAL EPITHELIAL CELLS

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Introduction Beta defensin-1 is an antimicrobial peptide released from epithelial cells, acting to defend the host against microbial activity and colonisation. It is possible that reduction in release of this antimicrobial peptide contributes to the host inability to remove bacteria from the airway. We investigated the release of beta-defensin-1 from the bronchial epithelium, with and without Non-Typeable *Haemophilus influenzae* (NTHi) infection and studied the effects of corticosteroids on this.
Method Human bronchial epithelial cells from three healthy donors were grown to 90% confluence. Cells were treated with 16 nM, 1.6 nM and 0.16 nM Budesonide or 10 nM, 1 nM and 0.1 nM Fluticasone propionate as per clinical equivalence, for two hours prior to addition of 1 × 106 CFU of NTHi. Cells were incubated for a further two hours. Beta-defensin-1 was measured in supernatants by ELISA.
Results NTHi infection downregulated beta-defensin-1 release by 42% (mean basal release: 133.6 pg/ml, SD: 61.6, mean release with NTHi infection: 77.6 pg/ml, SD: 50.6. p = 0.0084). Addition of Budesonide or Fluticasone propionate to bronchial epithelial cells decreased beta-defensin-1 release from mean basal level to 106.2 pg/ml (SD: 79.4, p = 0.023) and 100.6 pg/ml (SD: 50.0, p = 0.083) respectively. This release is synergistically decreased upon NTHi infection with Budesonide and Fluticasone propionate treatment (mean with NTHi: 67.3 pg/ml, SD: 38.7. p = 0.039 and 64.4 pg/ml, SD: 26.1. p = 0.048) respectively compared to corticosteroid treatment only. No difference in beta-defensin-1 level was seen between low and high dose of either corticosteroid tested.
Conclusion NTHi inhibits beta-defensin-1 release from healthy bronchial epithelial cells. This release is dampened further by corticosteroid treatment and may be implicated in NTHi persistence in the airway in patients with chronic lung disease such as COPD.

S104 HYPOXIA PRECONDITIONS THE INNATE IMMUNE RESPONSE TO ACUTE BACTERIAL PULMONARY INFECTIONS

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Introduction Systemic hypoxaemia and recurrent bacterial infections frequently co-exist in patients with acute and chronic lung disease and correlate with poor clinical outcomes. Inappropriate neutrophilic inflammation is regularly seen in these circumstances and the HIF/PHD pathway is implicated in the response of the innate immune system to both hypoxia and bacteria. Here we aimed to dissect and modify the interactions between hypoxia and innate host-pathogen response in the lung.
Methods C57BL/6 mice were either housed in room air or 'preconditioned' by being housed in 10% oxygen for 7 days. They then received intratracheal $1x10^7$ type 2 *S. pneumoniae* under recovery anaesthesia with subsequent exposure to hypoxia (10% O_2) or room air (21% O_2). Mice were assessed clinically, rectal temperatures recorded and culled for broncho-alveolar lavage (BAL) and tissue sampling (blood and lung) at various time points. Peripheral blood glucose was measured from tail vein venepuncture using a handheld blood glucose monitor. RNA from peripheral blood leucocytes was isolated and analysed using RNAseq. 18FDG-PET was performed on animals 14 h following infection to observe glucose utilisation. Histology was performed on formalin fixed sections for glycogen storage.
Results Exposure to acute hypoxia resulted in significant morbidity (sickness (5.7 vs 2.1, p < 0.02) and hypothermia (31.8 vs 36.0^0C, p < 0.05)) and rapid 100% mortality by 48 h post infection. This response was independent of bacterial burden, and leukocyte recruitment. In keeping with a negative energy state, hypoxic mice displayed loss of liver glycogen, with increased serum ketone production and lower circulating glucose levels. Preconditioned mice showed marked protection from both the acute hypoxia-associated systemic phenotype and the negative energy state. Transfer of preconditioned bone marrow to naïve mice also rescued the pathophysiological response. RNAseq analysis of the circulating leukocyte population identified signal-induced suppression of HIF-1a pathway genes, which were linked to reduced leukocyte glucose utilisation in vivo by 18FDG-PET.

Conclusions Hypoxic preconditioning reverses the morbidity and mortality associated with acute hypoxia following intrapulmonary bacterial challenge. This response is dependent on the preconditioning of the innate immune system by suppressing HIF1 alpha and altering circulating leukocyte metabolism.

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S105 PNEUMOCOCCAL SEROTYPES IMPLICATED IN ADULT PNEUMOCOCCAL PNEUMONIA, 9 YEARS FOLLOWING THE INTRODUCTION OF THE INFANT VACCINE PROGRAMME IN THE UK

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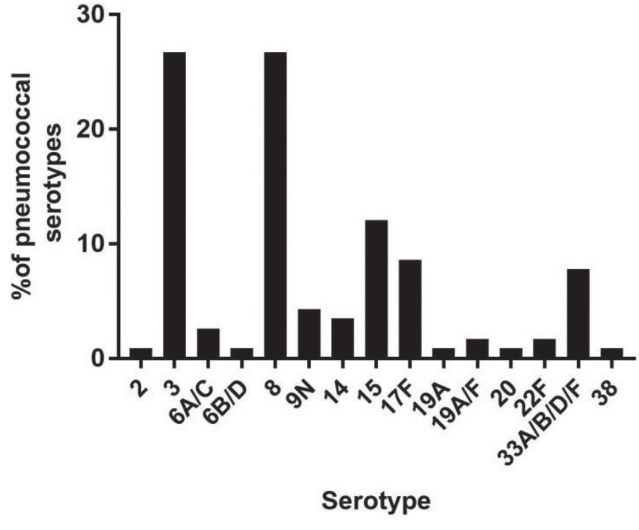
Background The introduction of the pneumococcal conjugate vaccines into infant vaccination schedules, has led to a change in the serotype prevalence causing adult pneumococcal disease, through the process of herd immunity. Whilst there are national surveillance programmes informing the changes in serotype in invasive pneumococcal disease, there are no comparable data to demonstrate the ongoing vaccine effect on non-invasive pneumococcal community acquired pneumonia (CAP), the most common clinical manifestation of pneumococcal disease in adults.

Methods Consecutive adult patients admitted to 2 hospitals, covering the catchment area of a large UK city, with a diagnosis of CAP were studied prospectively, over a 1 year period between September 2014 and 2015. A novel multiplex assay capable of detecting 24 serotypes/serogroups of *Streptococcus pneumoniae* was performed on patient urine. Pneumococcal infection was determined by identification of the organism from either sterile sites and/or detection of pneumococcal antigen or serotype in urine samples.



Abstract S105 Figure 1 Serotypes isolated in adult pneumococcal CAP

Results Of 478 individuals admitted with CAP, pneumococcal disease was diagnosed in 166 (34.7%) cases. Pneumococcal CAP diagnosis was made by blood culture, pneumococcal urinary antigen detection and urinary serotype detection in 23 (13.9%), 61 (36.8%) and 149 (89.8%) cases respectively. A definitive single serotype was identified in 116 individuals; the most commonly observed were serotypes 3 and 8 (31 cases each, 26.7%), followed by serogroup 15 (14 cases, 12.1%), 17F (10 cases, 8.6%) and 33A/B/D/E (9 cases, 7.8%).

Conclusion This is the first report on extended serotype distribution implicated in adult pneumococcal CAP, 9 years after the introduction of the UK infant vaccination programme. In this era of high infant vaccine coverage, whilst the majority of isolates are non-vaccine types due to the effects of serotype replacement, serotype 3 remains a common cause of adult pneumococcal CAP and may reflect inadequate serotype specific vaccine effectiveness.

S106 PERIPHERAL BLOOD NEUTROPHILS ARE PRIMED AND ACTIVATED IN BRONCHIECTASIS AND ARE ATTENUATED BY THE PRO-RESOLVING MEDIATOR LIPOXIN A4

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Introduction Excessive neutrophilic airways inflammation is the central feature of bronchiectasis but little is known about the role of serum neutrophils in bronchiectasis. Lipid mediators derived from arachidonic acid such as Lipoxin (LX)A4 are known to regulate the inflammatory process and generate pro-inflammatory, anti-inflammatory and pro-resolving mediators. In this research work, we propose to describe the function of peripheral neutrophils in bronchiectasis and the effect of LXA4.

Methods Three study groups were included in this study when clinically stable: 6 healthy volunteers; 6 patients with mild bronchiectasis with a Bronchiectasis Severity Index (BSI) score 0–4; 6 with severe bronchiectasis (BSI scores >9). Freshly isolated peripheral neutrophils from the groups were treated with LXA4 or vehicle control and we assessed spontaneous neutrophil apoptosis at 20 hours, neutrophil activation, neutrophil degranulation, phagocytosis of GFP labelled *Pseudomonas aeruginosa* and expression of LXA4 receptor formyl peptide receptor (FPR)2.

Results In vehicle treated neutrophils, there was increased viability and less apoptosis in bronchiectasis patients compared to healthy volunteers; Figure 1. There was a significant increase in CD11b upregulation; $p = 0.01$ and CD62L shedding; $p = 0.01$ in bronchiectasis patients compared to healthy volunteers. There was a significant increase in neutrophil degranulation with myeloperoxidase (MPO) release, in bronchiectasis patients; $p = 0.04$. There was an increase in neutrophil phagocytosis of GFP labelled *Pseudomonas aeruginosa* by neutrophils from bronchiectasis patients, $p = 0.03$, compared to healthy volunteers; Figure1.

In LXA4 treated neutrophils, there was no effect of LXA4 on spontaneous neutrophil apoptosis. There was a significant reduction in n-formyl-methyl-leucyl-phenylalanine (fMLF)-induced CD11b upregulation and CD62L shedding by LXA4 in a dose dependent manner in all three groups. There was a significant reduction in cytochalasin-B and fMLF-induced activation of neutrophils and release of MPO, by LXA4 in all three groups. There was significant improvement in neutrophil phagocytosis of GFP labelled *Pseudomonas aeruginosa* in a dose dependent manner in all three groups. There was a statistically significant increase in FPR2 receptor expression in healthy volunteers compared to bronchiectasis patients when treated with LXA4 100nM, $p = 0.03$.