which had been incubated in serum pre-treated with the enzyme IdeS (Immunoglobulin-G degrading enzyme of *S. pyogenes*, which selectively cleaves IgG). Complement deposition and neutrophil phagocytosis of unencapsulated *S. pneumoniae* TIGR4 strain was reduced in IdeS treated serum compared to untreated serum. These data demonstrate that there are naturally acquired functionally significant antibody responses to a range of conserved *S. pneumoniae* protein antigens. The same antigens induce responses in diverse populations, suggesting that these protein antigens would be useful components for a polyvalent protein vaccine that is broadly protective against *S. pneumoniae* infections.

S128 HIGHLY INVASIVE CAPSULAR SEROTYPES OF *STREPTOCOCCUS PNEUMONIAE* BIND HIGH LEVELS OF FACTOR H AND ARE RESISTANT TO COMPLEMENT AND PHAGOCYTOSIS

doi:10.1136/thoraxjnl-2011-201054b.128

¹C Hyams, ²K Trzcinski, ³D M Weinberger, ⁴M Lipsitch, ¹J S Brown. ¹Centre for Respiratory Research, UCL, London, UK; ²Department of Pediatric Immunology and Infectious Disease, University Medical Centre Utrecht, Utrecht, Netherlands; ³Division of International Epidemiology and Population Studies, National Institute of Health, Bethesda, Maryland, USA; ⁴Department of Epidemiology, Epidemiology and Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, USA

The *Streptococcus pneumoniae* polysaccharide capsule is an essential virulence factor that varies in structure between serotypes. While certain serotypes are highly invasive, it is unknown why these serotypes frequently cause infection yet others generally cause nasopharyngeal colonisation. Complement is vital in immunity to pneumococcus, and the capsule is known to affect complement deposition. Activation of the alternative complement pathway is promoted by factor B (Bf) binding, but inhibited by factor H (FH) activation. We hypothesised that capsule effects on FH and Bf interactions could alter *S. pneumoniae* complement sensitivity, partially explaining serotype-dependent differences in invasiveness. C3b/iC3b deposition, FH and Bf binding to *S. pneumoniae* were measured using flow cytometry assays on 20 distinct capsule-switch variants constructed on TIGR4 genetic background. These strains were therefore identical in protein structure, differing only in capsular serotype. Phagocytosis was investigated using an established flow cytometry assay, fresh human neutrophils and FAMSE labelled *S. pneumoniae*. FH binding showed wide variations between TIGR4-capsular switched strains, with a 7.5-fold difference between the highest (serotype2) and lowest (serotype11A) results. Differences in FH binding between strains did not correlate with capsular thickness, or with capsule structural motifs such as numbers of carbon atoms per repeating unit. FH binding negatively correlated with Bf binding and C3b/iC3b deposition, demonstrating that increased FH binding was associated with reduced alternative pathway activity and increased resistance to complement. IgG binding did not correlate with C3b/iC3b results, suggesting C3b deposition was independent of antibody-mediated complement activity. Neutrophil association correlated with C3b/iC3b deposition ($R^2=0.47$, $p=0.0008$) but negatively with FH binding ($R^2=0.74$, $p<0.0001$), confirming that high FH binding by pneumococcus was associated with reduced neutrophil phagocytosis. Weakly- and highly-invasive serotypes showed large significant differences between median C3b deposition ($p=0.007$), neutrophil association ($p=0.0002$) and FH binding ($p=0.0005$). Weakly-invasive serotypes had reduced FH binding, increased C3b/iC3b deposition and increased neutrophil association. Our novel finding that the degree of FH binding to *S. pneumoniae* capsular serotypes is associated with large variations in virulence offers a mechanistic explanation as to

why certain serotypes are more invasive than others. It also provides a potential in vitro method for identifying highly invasive strains.

S129 NEUTROPHIL FUNCTION AND ADVANCING AGE: THE EFFECTS OF SIMVASTATIN IN HEALTH AND DURING PNEUMONIA

doi:10.1136/thoraxjnl-2011-201054b.129

¹E Sapey, ¹H Greenwood, ¹J Hazeldine, ¹G Walton, ¹D Thickett, ¹J M Lord, ²R A Stockley. ¹University of Birmingham, Birmingham, UK; ²University Hospital Birmingham NHS Foundation Trust, Birmingham, UK

Background Age is associated with a decline in immunity, including neutrophil function. This may partially explain the worsening clinical outcomes seen following pneumonia in the elderly. Statins may improve outcomes from pneumonia although it is unknown whether they influence neutrophil function at conventional therapeutic concentrations. This is crucial, as statins may be beneficial adjuvants during infections.

Methods We studied the effect of 5 ng/ml Simvastatin (equivalent to 80 mg orally) on key neutrophil functions: speed and accuracy of migration using time-lapse imaging ($\mu\text{m}/\text{min}$), Neutrophil Extracellular Trap formation using cell-impermeable DNA-binding dye (in AFU) and generation of reactive oxygen species (ROS, in RLU).

Results We studied 70 healthy subjects (aged 20–90 years, 10 in each decennial) and 6 young (<35 years) and 6 older (>65 years) patients during an admission with pneumonia. All studied neutrophil functions declined with age (eg, neutrophil chemotaxis, $r=-0.7$, $p<0.001$). Specifically, average neutrophil chemotaxis for subjects >65 yrs was $0.72 \mu\text{m}/\text{min}$ (SD ± 0.28 , $p<0.001$) slower than subjects <35. These neutrophils produced less NETS (average difference $=-1725\text{AFU}\pm 283$, $p=0.007$) and peak ROS (average difference $=-117\text{RLU}\pm 31$; $p=0.04$). Neutrophils from young patients with pneumonia displayed an up-regulation of function that was not seen in older pneumonia patients. There were no age-associated differences in the surface expression of chemo-attractant receptors, but there appears to be differential intracellular signalling with reduced expression of adhesion molecules. Incubating neutrophils from older subjects with Simvastatin improved all functions back to that seen in young subjects (chemotactic speed $+0.92 \mu\text{m}/\text{min} \pm 0.27$, $p=0.001$; NET $+1386\text{AFU}\pm 273$, $p=0.04$; ROS $+223\text{RLU}\pm 39$, $p=0.005$). Similar improvements were seen with neutrophils from older subjects with pneumonia. This was a dose-dependent phenomenon; not seen at higher concentrations of Simvastatin.

Conclusion With age, there is a global deterioration in neutrophil function and no up-regulation when pneumonia is present, which may partially explain the age-associated mortality. Simvastatin up-regulates neutrophil function in the elderly, even during pneumonia. This up-regulation may explain the beneficial effects seen clinically. In vivo studies are warranted, to determine if simvastatin should be utilised during episodes of acute infection.

S130 HIV-1 INFECTION OF MACROPHAGES DYSREGULATES PRO-INFLAMMATORY HOST RESPONSES TO MYCOBACTERIUM TUBERCULOSIS THROUGH INHIBITION OF INTERLEUKIN 10

doi:10.1136/thoraxjnl-2011-201054b.130

¹G S Tomlinson, ²P T G Elkington, ¹L Bell, ²N F Walker, ¹J Tsang, ¹J Brown, ¹R Breen, ¹M Lipman, ¹D R Katz, ¹R F Miller, ¹B M Chain, ¹M Noursadeghi. ¹University College London, London, UK; ²Imperial College London, London, UK

Introduction Human immunodeficiency virus (HIV)-1 greatly increases the risk of active *Mycobacterium tuberculosis* (Mtb)