Introduction Early diagnosis of lung cancer improves survival and strategies to facilitate this include screening high risk populations. The ongoing UK Lung Screen Trial (UKLS) is investigating this with low-dose CT scans, and positive screens are referred to clinical services for further investigation and treatment. We report the outcome for such cases referred to our large lung cancer unit.
Methods The UKLS reporting radiologists code scans according to their abnormality: local patients with features suspicious for malignancy (category 4) are referred to our MDT, where following counselling they undergo appropriate investigation.
Results We have received 37 referrals (mean age68 [range 61–75], median performance status 1, mean FEV1 78% predicted [33–107], 27 male) during the first 14 months of the trial.

In 23 cases (62%) subsequent investigation confirmed malignancy (11 adenocarcinoma, 8 squamous cell carcinoma, 3 small cell carcinoma, 1 mesothelioma). In 14 cases where malignancy was not confirmed all had been referred for additional investigations (including 3 PET-CT scans, 5 bronchoscopies and 8 CT scans):1 patient underwent wedge resection of a PET positive lesion (granulomatous process) and 13 remain under follow-up for nodule surveillance.

Twenty of those with malignancy (87%) were potentially operable (median stage 1A, mean age 68 [range 61–74], median performance status 1, mean FEV1 80% predicted [33–107], 13 male), including 2 with limited stage small cell carcinoma. Overall, 19 patients were treated by lobectomy with curative intent. The remaining 4 cases all received oncological management.
Discussion The UKLS is the first large randomised controlled trial to assess a CT-based screening protocol for lung cancer in the United Kingdom. We have shown that the majority of referrals from this programme were confirmed as cases of lung cancer of which nearly all were operable. Such screening programmes will help us improve the prognosis in this previously late-diagnosed and often incurable disease.

COPD: mechanisms of host defence

S111 HUMAN RHINOVIRUS INFECTION AND EXACERBATION FREQUENCY AT COPD EXACERBATION

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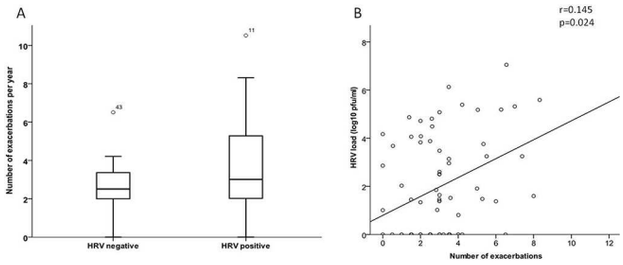
Introduction Viral infections are associated with more severe COPD exacerbations in terms of greater burden of symptoms, resulting in longer recovery times and a greater likelihood of hospitalisation (Seemungal *et al*. 2000). Human rhinoviruses (HRV) are the main aetiological agents of virus-associated COPD exacerbations; however the association of HRV infection and exacerbation frequency has not been fully investigated. We aimed to examine the relationship between HRV presence and load, and the number of exacerbations patients experienced per year.
Methods London COPD cohort patients recorded any new or increased respiratory symptoms on daily diary cards and contacted the clinical team when symptoms worsened. Exacerbations were defined using our usual symptomatic criteria; an increase in respiratory symptoms for two consecutive days, with at least one symptom being major (dyspnoea, sputum purulence or volume). Reverse-transcription quantitative PCR was used to detect HRV prevalence and load in sputum samples collected at exacerbation presentation (median 2 days after exacerbation onset).
Results Patients positive for HRV (n = 42) had significantly more exacerbations per year than those without HRV (n = 31); the median (IQR) number of exacerbations per year in those with HRV infection was 3.01 (2.02–5.30) which was significantly greater than those without HRV infection 2.51 (2.00–3.51); p = 0.038 (Figure 1A). At exacerbation, a higher HRV load significantly correlated with the number of exacerbations patients experienced per year; r = 0.145; p = 0.024 (Figure 1B).
Conclusion Patients with positive HRV infection at the time of exacerbation had experienced more exacerbations per year than those who did not have HRV. In patients with a higher exacerbation frequency, the HRV load at exacerbation was greater suggesting that patients with a history of frequent exacerbations are more susceptible to viral infection. This susceptibility may provide the mechanisms for the development of the frequent exacerbator phenotype. Thus these findings emphasise the importance of preventing viral infections and exacerbations in COPD patients.



Abstract S111 Figure 1. (A) The number of exacerbations per year in patients with HRV (n = 42) was significantly higher than in those without HRV (n = 31), p = 0.038. (B) There was an association between the number of exacerbations had by patients per year and the HRV load (r = 0.145; p = 0.024).

S112 HDAC ACTIVITY IN MACROPHAGES IN EXPERIMENTAL RHINOVIRUS INFECTION IN COPD

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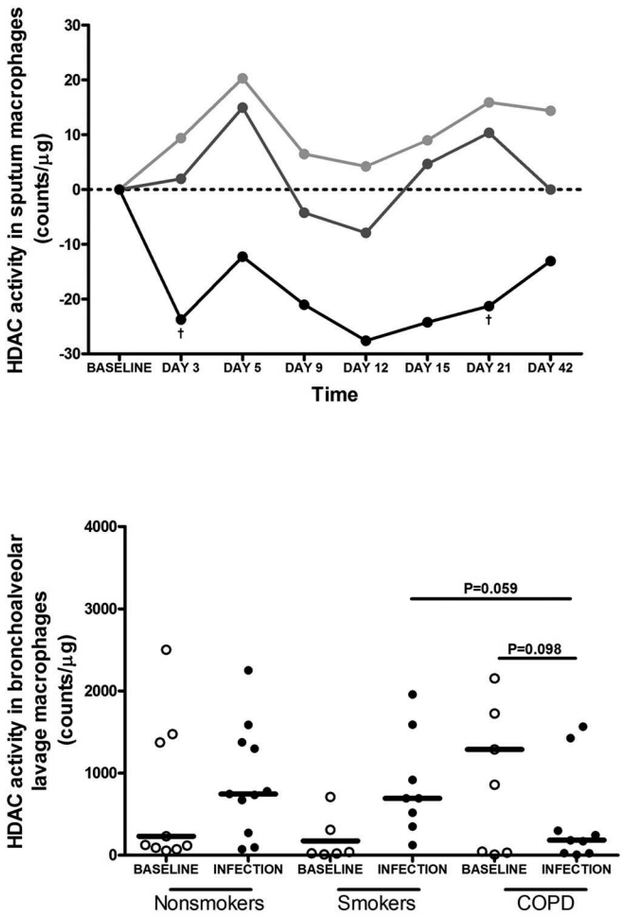
Introduction and Objectives Acute exacerbations are a major cause of morbidity and mortality in COPD and current treatments are not very effective. Histone deacetylase 2 (HDAC2) is deficient in stable COPD and is likely to be a mechanism of corticosteroid resistance. It is not known whether impaired HDAC2 activity is an important mechanism in COPD exacerbations.
Methods 9 subjects with GOLD stage II COPD, 10 smokers and 11 non-smokers were infected with rhinovirus 16. Macropahges from induced sputum and bronchoalveolar lavage (BAL) were collected before and following rhinovirus infection and HDAC2 activity measured. Virus load and inflammatory markers were measured in sputum supernantants.
Results At baseline there were no differences in HDAC2 activity in sputum or BAL macrophages between the groups. Following infection HDAC2 activity in the smoking controls and non-smoking controls did not change significantly from baseline (Figure 1). In the COPD subjects there was a trend towards reduced HDAC2 activity in both sputum (ANOVA P = 0.064) and BAL macrophages (Paired t test P = 0.098). Sputum HDAC activity



Abstract S112 Figure 1.

was significantly lower in the COPD subjects compared to non-smokers on days 5 and 42 (P < 0.05), and there was a trend towards lower levels of HDAC in BAL macrophages at infection compared to the non-smokers (P = 0.095) and smokers (P = 0.059) (Figure 1).

Lower sputum macrophage HDAC2 activity at baseline was associated with greater sputum virus load (r = -0.82, P = 0.022) and higher sputum levels of neutrophil elastase (r = -0.81, P = 0.022) and TNF- (r = -0.79, P = 0.028).HDAC2 activity in BAL macrophages at infection correlated inversely with peak NL virus load (r = -0.8, P = 0.0096), peak sputum GM-CSF (r = -0.67, P = 0.0499), TNF- (r = -0.72, P = 0.03), neutrophil elastase (r = -0.67, P = 0.0499) and sputum nitrite levels (r = -0.78, P = 0.0125).

Conclusions Following rhinovirus infection HDAC2 activity in airway macrophages is reduced and relates to airway inflammatory markers. Restoring HDAC activity is a potential therapeutic option for COPD exacerbations.

S113 HAEMOPHILUS INFLUENZAE STIMULATION OF ALVEOLAR MACROPHAGES FROM COPD PATIENTS; EFFECTS OF CORTICOSTEROIDS

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Background The lower airways of COPD patients are often chronically colonised by bacteria such as Non-typeable *Haemophilus influenza* (NTHI). Bacteria are a common cause of COPD exacerbations. Corticosteroids are often used to prevent and treat COPD exacerbations.

The aim of this study was to investigate the effect of corticosteroids on the *in vitro* inflammatory response of COPD alveolar macrophages (AM) to NTHI infection. We also investigated the cell signalling pathways activated by NTHI infection.

Methods AM from 12 COPD patients and 9 smoking controls were infected with live NTHI at multiplicity of infection (MOI) of 100:1 (bacteria: AM) for 24 hours. AM were pre-treated with dexamethasone (up to 1 M) for 1 hour. Supernatants were analysed for TNF- , IL-6, IL-8 and IL-10 by ELISA. AM protein was extracted for Western blot analysis of nuclear factor B (NF B), p38 and extracellular regulated mitogen activated protein kinases (p38 and ERK) activation.

Results NTHI stimulated release of TNF- , IL-6, IL-8 and IL-10 (p < 0.05) from both COPD patients and controls.

TNF- , IL-6 and IL-10 production was significantly inhibited by dexamethasone at 1 and 0.1 M (p < 0.05). Inhibition of TNF- and IL-6 release was significantly higher in AM from smokers compared to COPD patients. Dexamethasone had no effect on IL-8 production (see table 1).

NTHI infection activated NF B, p38 and ERK MAPK signalling pathways in AM.

Conclusion NTHI infection stimulated COPD AM to release inflammatory cytokines which are only partially responsive to corticosteroids; importantly, there was no suppression of the neutrophil chemoattractant IL-8. The production of this corticosteroid resistant chemokine is associated with NF- B and MAPK activation; these signalling pathways drive bacteria induced inflammation in COPD airways.

Abstract S113 Table 1. Dexamethasone inhibition of NTHI induced mediator production in alveolar macrophages.

	Percentage inhibition by 1 M dexamethasone	
Cytokine	**COPD**	**Smokers**
TNF-	42.5% ***#	67.3% ***#
IL-6	26% **#	43.2% **#
IL-8	-29%	16.2%
IL-10	44% ***	38.7% **

,* = significant bellow dimethyl sulfoxide (DMSO) control (p< 0.01, 0.001)
= significant difference between COPD and Smokers (p<0.05)

S114 SIMVASTATIN IMPROVES NEUTROPHIL MIGRATORY TARGETING IN COPD: *IN VITRO* STUDIES SUPPORTING STATIN USE AS A POTENTIAL ADJUVANT THERAPY

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Introduction Statin use in COPD is associated with a reduction in all cause mortality, with greatest reductions seen in patients with the highest inflammatory burden. However, the mechanism for these effects is poorly understood, as statin treatment has not been found to lower systemic inflammation and *in vitro* studies of cellular effects use concentrations that exceed the therapeutic range. Neutrophils are key effector cells in COPD, and correlate with disease severity and inflammation. Recent *in vitro* studies