common in patients aged >65 (p = 0.048). Anxiety appeared more common in females, but this did not reach statistical significance. The presence of depression and anxiety was not related to severity of lung disease as measured by KCO, FVC or oxygen saturations.
Conclusions Use of a simple self-administered screening tool can identify high levels of anxiety and depression in outpatients with interstitial lung disease. Anxiety levels are more common in elderly patients. Identifying psychological problems in this patient group may allow development of new therapeutic options so physicians can improve patient's symptoms and quality of life. Psychopharmacology, cognitive behavioural therapy or pulmonary rehabilitation may be possible treatment options and merit further study.

S5 PHYSIOLOGICAL DETERIORATION VS STABILISATION IN MYOSITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE: PHENOTYPIC DIFFERENCES AND INFLUENCE OF IMMUNOSUPPRESSIVE TREATMENT

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Background Interstitial lung disease (ILD) may form a prominent component of idiopathic inflammatory myositis (IIM) and even dominate the clinical course of disease. We observed that certain characteristics were associated with longitudinal worsening of lung disease, including temporal differences that suggest that particular patterns of ILD progression may be expected.
Methods Patients on the St George's Hospital Myositis database with polymyositis (PM), dermatomyositis (DM), overlap syndrome or antisynthetase (Jo-1) syndrome with associated pulmonary abnormalities (as confirmed by CT) were identified. Stable lung disease was accepted as a ⩽10% decrease in forced vital capacity (FVC) and/or a ⩽15% decrease in diffusing capacity (DLCO) over the first year of diagnosis.
Results 20 patients with IIM-ILD were identified (mean FVC 70±18% predicted, mean DLCO 50±17% predicted at diagnosis). Mean duration of myositis follow-up was 10.75±6.4 years. 17 of 20 (85%) had ⩾2 measurements of pulmonary function tests (PFTs), with an average total PFT follow-up of 4.7 years. DLCO decline was evident in 7 patients, against a stable/improved pattern in 10 others. Deteriorators tended to have a greater decline in DLCO in their first year of follow-up (−13±13 vs +26±40 for stable patients p = 0.06). Overall, most patients who experienced early PFT deterioration continued to do so thereafter, albeit at a variable rate. For most, an established decline in DLCO at 3 years from diagnosis heralded further loss subsequently. Deteriorators tended to be younger and more commonly reported respiratory symptoms at initial diagnosis. Amongst them, DM was the most common myositis (5/7, 71%), in contrast to 8/10 (80%) of stable patients with PM (p = 0.008). Afro-Caribbean ethnicity was also more frequent in those with IIM-ILD but did not distinguish deteriorators from stabilisers. Patient numbers were inadequate for ascribing clinical significance to specific ILD patterns.
Conclusions For most patients with myositis, ILD is a relatively benign complication that is satisfactorily controlled by immunosuppressive therapy. In those with progressive lung disease, loss of DLCO appears to be a crucial consequence. These individuals more commonly have DM, are younger and have a shorter duration of lung disease. PFT stabilisation following early deterioration is occasionally apparent, although the long-term significance of this observation remains unclear.

Abstract S5 Table

	Deteriorators	Stabilisers	
	n = 7	n = 10	p Value
Age at diagnosis	39±15	50±19	0.18
Ethnicity			
Black	4 (57%)	5 (50%)	
White	1 (14%)	5 (50%)	0.14
Other	2 (29%)	0	
ILD pattern on HRCT			
UIP	2 (29%)	4 (40%)	
NSIP	5 (71%)	4 (40%)	0.33
OP	0	2 (20%)	
Presence of lung disease at initial presentation	5 (71%)	3 (30%)	0.15
Muscle disease			
Polymyositis (PM)	1 (14%)	8 (80%)	
Dermatomyositis (DM)	5 (71%)	1 (10%)	0.008
Other	1 (14%)	1 (10%)	
ANA positive	5 (71%)	6 (60%)	1.0
Death	1 (14%)	4 (40%)	0.34
% change in PFTs over first year			
FVC	+7±21%	+17±30	0.48
DLCO	−13±13%	+26±40	0.06
TLC	−2±22%	+3±13	0.66
% change in PFTs over total duration of follow-up			
FVC	−1±52%	+12±21	0.56
DLCO	−31±15%	+10±20	0.002
TLC	−10±26%	+2±15	0.37

ANA, antinuclear antibody; DLCO, diffusing capacity; FVC, forced vital capacity; HRCT, high-resolution CT; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia; PFT, pulmonary function test; TLC, total lung capacity; UIP, usual interstitial pneumonia.

Cellular interactions in the pathogenesis of pulmonary hypertension

S6 REGULATION OF ENDOTHELIN-1 PRODUCTION BY THE TRANSFORMING GROWTH FACTOR/BONE MORPHOGENETIC PROTEIN PATHWAY IN HUMAN PULMONARY ARTERY SMOOTH MUSCLE CELLS

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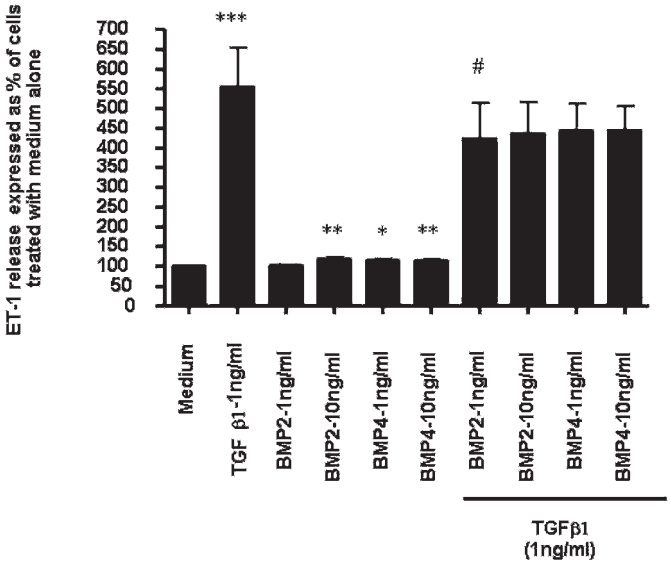
Background Pulmonary artery hypertension is a fatal condition associated with remodelling of pulmonary resistance vessels. There is convincing evidence for the involvement of both the transforming growth factor β (TGFβ)/bone morphogenetic protein (BMP) and endothelin (ET-1) pathways in this remodelling process. However, it is unknown how these two pathways interact.
Aim To investigate the effect of TGFβ1, BMP2 and BMP4 on ET-1 release from normal human pulmonary artery smooth muscle cells (HPASMCs).
Methods HPASMCs were grown from resected and morphologically normal pulmonary arteries taken from patients with lung cancer at the Royal Brompton Hospital. Cells were treated with TGFβ1 and/or BMP2 and BMP4 (0, 1 and 10 ng/ml). Following 24 h incubation supernatants were collected and ET-1 concentrations determined by ELISA (R&D, Abingdon, UK). Data were analysed using Student t test.
Results TGFβ1 dose dependently increased ET-1 release from HPASMCs. TGFβ1 (1 ng/ml) significantly increased ET-1 generation by 553% compared with cells treated with medium alone (fig 1; n = 6)). BMP2 (10 ng/ml) and BMP4 (1 and 10 ng/ml) also



Abstract S6 Figure 1 The effect of transforming growth factor β (TGFβ), bone morphogenetic protein 2 (BMP2) and BMP4 alone or in combination on endothelin (ET-1) release. Data are from 3–6 donors where ***$p<0.001$, **$p<0.01$. *$p<0.05$ compared with cells treated with medium. # indicates $p<0.05$ compared with cells treated with TGFβ1 alone.

significantly promoted ET-1 release by up to 20% compared with controls (fig 1; n = 6). When HPASMCs were co-treated with TGFβ1 and BMP2 or BMP4 there was a trend for BMP2 (10 ng/ml) and BMP4 (1 and 10 ng/ml) to attenuate TGFβ1-induced ET-1 release, with only BMP2 at 1 ng/ml significantly inhibiting this release by 24% (fig 1; n = 3).

Conclusion These findings suggest that there may be significant cross-talk between TGFβ/BMP and ET-1 in HPASMCs. Further work is needed to investigate the effect of bone morphogenetic protein type II receptor (BMPR-II) mutations on ET-1 release.

S7 TUMOUR NECROSIS FACTOR α, BONE MORPHOGENETIC PROTEIN 9 AND CICLOSPORIN AFFECT EXPRESSION OF BONE MORPHOGENETIC PROTEIN TYPE II RECEPTOR IN HUMAN PULMONARY ARTERY ENDOTHELIAL CELLS: POTENTIAL ROLES IN THE PATHOGENESIS OF PULMONARY ARTERIAL HYPERTENSION

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Introduction and Objectives Mutations in the bone morphogenetic protein type II receptor gene (BMPR-II) are central to the pathogenesis of familial pulmonary arterial hypertension (PAH). They are found in 70% of familial and up to 40% of sporadic cases. In both familial and sporadic cases, BMPR-II expression is reduced irrespective of whether the BMPR-II gene is mutated or not. These findings suggest that the BMPR-II gene promoter and its regulation may play a key role. This study aimed to determine key pathways that affect BMPR-II gene expression in human pulmonary artery endothelial cells (HPAECs). Previous experiments in HeLa cells assessed a range of mediators and identified the inflammatory cytokine tumour necrosis factor α (TNFα) as a repressor of BMPR-II promoter activity. Inflammation has been widely implicated in the process of pulmonary vascular remodelling and we hypothesised that TNFα and other inflammatory cytokines decrease BMPR-II expression in disease-relevant cells, namely HPAECs.

Methods HPAECs were cultured to confluence, serum starved, and exposed to a panel of cytokines and growth factors implicated in cell signalling or vascular remodelling. Reagents which altered BMPR-II mRNA levels 2-fold were identified in reverse transcription-PCR (RT-PCR) screens, then tested more extensively by quantitative PCR (qPCR) and western blotting.

Results Angiotensin II, ciclosporin (CSA), β-oestradiol, bone morphogenetic protein 9 (BMP9), TNFα and thrombin significantly altered BMPR-II mRNA levels in screening experiments. However, only BMP9, CSA and TNFα significantly altered BMPR-II expression when the experiment was repeated in triplicate. BMP9 increased expression 8.74-fold, whereas CSA and TNFα decreased expression >2-fold. This was reproduced in western blotting.

Conclusions TNFα, BMP9 and CSA may be important regulators of BMPR-II expression. Further experiments are needed to establish whether this occurs through BMPR-II promoter binding and to identify important regulatory regions. The effect of TNFα on BMPR-II expression is in keeping with our previous findings in HeLa cells and with the inflammatory model of PAH. These results highlight the importance of controlling inflammation in primary and secondary prevention of PAH and may also provide future pharmacological targets.

S8 TRAIL EXPRESSION IS INCREASED IN THE RAT MONOCROTALINE MODEL OF PULMONARY ARTERIAL HYPERTENSION

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Introduction and Objectives Despite improvements in the overall management of pulmonary arterial hypertension (PAH) the disorder still causes significant morbidity and mortality. Better insight into the molecular pathogenesis of pulmonary vascular remodelling could lead to the development of more targeted therapeutics. There is emerging evidence to support that tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) plays an important role in vascular biology. We were recently the first to demonstrate that TRAIL expression is upregulated within pulmonary vascular lesions of patients with idiopathic PAH. Moreover we have demonstrated that recombinant human TRAIL induces the proliferation and migration of human pulmonary artery smooth muscle cells (HPASMCs). The aim of this current study was to determine the expression profile of TRAIL through disease progression utilising the rat monocrotaline (MCT) model of PAH.

Methods Male Sprague–Dawley rats (200–260 g, n = 7 per group) were injected with either MCT (60 mg/kg) or saline as control. They subsequently underwent haemodynamic studies, with harvesting of serum, heart and lungs at day 2, 7, 14, 21 and 28 after injection. Segments of lung were immediately snap-frozen in liquid nitrogen for subsequent determination of TRAIL protein by western immunoblotting and subsequent densitometry with normalisation to β-actin.

Results A significant increase in right ventricular maximum dP/dT was observed 14 days after treatment with MCT. Right ventricular hypertrophy (RVH) and right ventricular systolic pressure (RVSP) developed, and remained significantly elevated from 21 days in the MCT-treated rats. The levels of TRAIL protein in whole lung protein lysates showed a trend for an increase at day 21 and were significantly higher at 28 days in the MCT-treated rats.

Conclusion TRAIL protein is upregulated in the rat MCT model of PAH but only in the latter stages of disease. Work is ongoing to determine the profile of TRAIL RNA expression in the lung, serum levels of TRAIL, and the localisation of TRAIL within the pulmonary vascular lesions of this model.

S9 OSTEOPROTEGERIN EXPRESSION IS INCREASED PRIOR TO HAEMODYNAMIC ALTERATIONS IN THE RAT MONOCROTALINE MODEL OF PULMONARY ARTERIAL HYPERTENSION

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Introduction and Objectives Pulmonary arterial hypertension (PAH) is a life-threatening condition with high morbidity and poor life expectancy. Pathologically, PAH is characterised by pulmonary artery medial thickening, fibrosis and, in some cases, plexiform lesions. Better insight into the molecular pathogenesis of this process could lead to the development of novel targeted therapeutics. We have recently demonstrated that the secreted glycoprotein osteoprotegerin (OPG, TNFRSF11B) is increased both within lesions and in serum from patients with idiopathic PAH. We have also shown that OPG promotes the proliferation and migration of pulmonary artery smooth muscle cells and hypothesise that OPG plays an important role in the pathogenesis of PAH. The aim of this study was to determine the temporal expression profile of OPG during disease progression utilising the rat monocrotaline (MCT) model of PAH.

Methods Male Sprague–Dawley rats (200–260 g, n = 7 per group)-were injected with either MCT (60 mg/kg) or saline as control. Cardiac catheterisation was performed to measure haemodynamic parameters prior to collection of serum and heart and lung tissue at day 2, 7, 14, 21 and 28 after treatment. OPG was measured in serum by sandwich ELISA and in whole lung protein lysates by western immunoblotting with normalisation to β-actin.

Results A significant increase in right ventricular maximum dP/dT was observed from 14 days after treatment with MCT, right ventricular hypertrophy (RVH) and right ventricular systolic pressure (RVSP) developed, and remained significantly elevated from 21 days in the MCT-treated rats. There was a trend for increased levels of serum OPG from day 7 and a significant increase from 14 days in MCT-treated rats. OPG protein expression within whole lung showed a trend towards an increase from 7 days and reached significance at 21 days in the MCT-treated rats.

Conclusion These data provide further evidence that OPG may be important in the pathogenesis of PAH. Serum OPG increased prior to haemodynamic changes in this model, suggesting that OPG may also be a useful biomarker for the early stages of PAH. Further studies are underway to determine whether OPG itself may be a target for therapy in PAH.

S10 REGULATION OF EXPRESSION AND FUNCTION OF OSTEOPROTEGERIN IN PULMONARY ARTERY SMOOTH MUSCLE CELLS IN VITRO

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Introduction and Objectives Pulmonary arterial hypertension (PAH) is characterised pathologically by the obliteration of small arteries in the lung. Abnormal proliferation and migration of pulmonary artery smooth muscle cells (PASMCs) is key to this process. There are now well-established links between bone morphogenetic protein receptor type II (BMPR-II) mutations, the serotonin (5-hydroxytryptamine (5-HT)) pathway and inflammatory mechanisms in this process. We have recently reported that osteoprotegerin (OPG), also known as TNFRSF11B, is upregulated in serum and lesions of patients with idiopathic PAH. We have also shown that OPG induces both proliferation and migration of PASMCs in vitro. We hypothesise that OPG plays a central role in, and contributes to the pathogenesis of PAH. We now aim to determine the regulation of expression of OPG in PASMCs.

Methods Primary human PASMCs (Cascade Biologics) were used for all studies. Recombinant OPG and interleukin-1 (IL-1) were purchased from R&D Systems and 5-HT from Sigma. OPG mRNA levels were quantified using TaqMan PCR. Intracellular protein was assessed by western immunoblot, and conditioned medium was assayed by sandwich ELISA. To analyse the downstream signalling, protein lysates were isolated after 5, 10 and 60 min incubation with 50 ng/ml OPG.

Results OPG mRNA expression was raised at 4 h poststimulation with IL-1β and 5-HT. Intracellular OPG levels were increased following IL-1β and 5-HT stimulation at 24 and 48 h. OPG secretion into the culture medium significantly increased from 24 h poststimulation, suggesting that OPG is rapidly released from cells following translation. Stimulation with TGFβ increased OPG within conditioned media; however, no increase in either mRNA or intracellular protein was detected. Stimulation of PASMCs with OPG resulted in a significant increase in extracellular signal-regulated kinase (ERK) 1/2 phosphorylation at 5 min.

Conclusions We have demonstrated that signals from multiple pathways associated with PAH converge upon, and stimulate the expression and release of OPG from PASMCs. OPG induces the phosphorylation of ERK 1/2, and PASMC proliferation and migration. Further work is ongoing to establish whether ERK 1/2 phosphorylation is required for OPG-induced proliferation and migration.

S11 FAT-FED APOE/IL-1R1 DOUBLE-DEFICIENT MICE ARE PROTECTED FROM ATHEROSCLEROSIS BUT DEVELOP SEVERE PULMONARY HYPERTENSION

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Introduction and Objectives Pulmonary arterial hypertension (PAH) is a life-threatening condition with high morbidity and poor life expectancy. Inflammatory mechanisms are proposed to play a significant role in disease progression, particularly PAH associated with other diseases—for example, systemic sclerosis. Previous studies have demonstrated that members of the interleukin family of inflammatory cytokines are upregulated in PAH; treatment of rats with the interleukin-1 (IL-1) receptor antagonist has been shown to protect against development of monocrotaline-induced PAH, and IL-6 overexpression has been show to induce PAH in mice. Our group has recently demonstrated that ApoE$^{-/-}$/IL-1R1$^{-/-}$ mice have reduced diet-induced atherosclerosis and lower systemic blood pressure compared with ApoE$^{-/-}$ mice on the same diet. Since fat-fed ApoE$^{-/-}$ mice have been shown to develop pulmonary hypertension, we hypothesised that ApoE$^{-/-}$/IL-1R1$^{-/-}$ mice would exhibit a reduced PAH phenotype.

Methods ApoE$^{-/-}$ and ApoE$^{-/-}$/IL-1R1$^{-/-}$ mice were fed either regular chow or Paigen diet for 8 weeks prior to echocardiography, right and left heart cardiac catheterisation and serum and tissue harvest to assess pulmonary hypertension phenotype.

Results The Paigen-fed ApoE mice developed increases in right ventricular systolic pressure (RVSP) in line with published data. Surprisingly, the ApoE$^{-/-}$/IL-1R1$^{-/-}$mice exhibited higher pressures (mean 75 mm Hg, $p<0.05$ n = 6). This finding was matched by significant increases in right ventricular hypertrophy compared with chow-fed controls. Analysis of lung sections by α-smooth muscle actin immunohistochemistry also revealed muscularisation of the distal pulmonary arteries. We have previously reported that high serum levels of osteoprotegerin (OPG) are associated with PAH in humans; this increase also correlates with development of PAH in

our rat models. The ApoE$^{-/-}$ fat-fed mice exhibited a 2-fold increase ($p<0.001$, $n = 9$), and the ApoE$^{-/-}$/IL-1R1$^{-/-}$ animals a 4-fold increase ($p<0.0001$, $n = 5$) in serum OPG compared with chow-fed controls.

Conclusions These studies further implicate IL-1 signalling in PAH; however, the mechanisms remain unclear. The data also support a role for OPG in PAH. Additional studies are underway to examine other key inflammatory pathways to determine whether they compensate for the lack of IL-1 signalling in this model, and so drive disease pathogenesis.

Tuberculosis screening: variations on a theme

S12 SYSTEMS BIOLOGY APPROACHES CHARACTERISE THE HOST RESPONSE TO TUBERCULOSIS

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Introduction Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. The immune response during TB is complex and incompletely characterised, hindering the development of new diagnostics, treatments and vaccines. Studies performed in different disease settings (intermediate vs high burden) have sometimes yielded divergent results, limiting advances in our understanding of TB. We used systems biology approaches to obtain an unbiased comprehensive survey of the host response to TB in both the UK and South Africa.

Methods We recruited 214 participants; 153 met the final inclusion criteria. Active TB patients were culture positive. Latent TB patients were positive by both tuberculin skin test (TST) and interferon γ release assay (IGRA), and healthy controls were negative by both TST and IGRA. Whole blood was collected before treatment. RNA was extracted and used for whole genome expression studies using Illumina HT-12 microarrays. This was complemented by multiplexed cytokine analysis using the MILLIPLEX Multi-Analyte Profiling system. Biological data were integrated with comprehensive clinical data including radiology. Data mining was performed using Genespring GX 7.3 and Ingenuity Pathways Analysis software in combination with a novel Genomic Modular Analysis Framework. A subset of patients was assessed at 2 and 12 months post-treatment.

Results 42 participants from London were used as a training set to explore the microarray data, using supervised and unsupervised analyses to define a transcriptional signature. Findings were then tested in an independent set of 53 participants from London, and further validated using an independent cohort of 56 South African patients. We thus identify a robust blood transcriptional signature for active TB in both intermediate and high burden settings. Analysis of blood leucocyte counts and serum cytokines, along with interrogation of gene expression data using Pathway and Modular analysis, suggests that this signature reflects changes in cellular composition and altered cytokine expression. Transcriptional profiles appeared to reflect disease status. Longitudinal analysis revealed that the signature of active TB disappears during successful treatment.

Conclusions This is the first whole-genome expression profiling study in human TB. Our findings have implications for understanding disease pathogenesis, and could yield biomarkers for diagnosis and treatment monitoring.

S13 CONTACT SCREENING WITH SINGLE-STEP TIGRA TESTING AND RISK OF ACTIVE TB INFECTION: THE LEICESTER COHORT ANALYSIS

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Introduction A policy of a systematic single-step T cell-based interferon γ release assay (TIGRA) with QuantiFERON-TB Gold (QTG) has been employed at Leicester to screen for latent tuberculosis infection (LTBI) in close TB contacts since January 2007. Twelve week chemoprophylaxis is offered to all healthy QTG +ve contacts <35 years old. Baseline and longitudinal data have been collected prospectively for all index cases and their associated contacts since the introduction of the policy. Here we present the results of a cohort study examining outcome with QTG testing in all contacts since 2007.

Methods Data from all recorded contacts of patients with active TB diagnosed after 1 January 2007 are included. Contacts that developed active TB during the follow-up period were labelled ''converters'' if no evidence of active disease was identified at screening. Conversion risk was estimated using Kaplan–Meir plots and compared between defined subgroups using the log-rank test.

Results 2204 contacts (mean age 31.6 years, 51% male) were recorded in 446 notified cases (mean 4.9 contacts per case). 1039 contacts (47.1%) underwent screening with QTG and 204 were QTG +ve (19.6%). The mean follow-up period in QTG screened and unscreened contacts was 435 (±212) days and 455 (±235) days, respectively ($p = 0.88$). Chemoprophylaxis was started in 173 contacts (54 QTG untested). No QTG –ve contacts received chemoprophylaxis. Twelve week adherence was achieved in 90 contacts (52%). There were 39 converters (20 in the QTG-screened group). Of these, two had received chemoprophylaxis but only one had completed 12 weeks. All converters in the QTG tested group were QTG +ve. Two-year conversion risk (95% CI) in contacts not receiving chemoprophylaxis was 1.6% (0.8% to 2.4%) in the QTG untested population and 17.2% (9.4–25%) in QTG +ve contacts (hazard ratio (HR) = 10.3 if QTG +ve). Chemoprophylaxis lowered 2-year conversion risk in QTG +ve contacts to 4.7% (2.9% to 6.4%; HR 9 if no chemoprophylaxis).

Conclusion We estimate that 1 in 7.8 contacts testing QTG +ve will develop active TB without prophylaxis. QTG testing is an effective screening tool for identifying contacts at high risk of conversion.

S14 NEW ENTRANT SCREENING FOR LATENT TUBERCULOSIS USING IGRA TESTING ALONE

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Background Our Local Government area has predominantly (but not exclusively) immigration from South Asia (India, Pakistan and Banglasdesh). Prior to 2006 these were screened for latent tuberculosis infection as per then Joint Tuberculosis Committee 2000 Guidance. Following the National Institute for Health and Clinical Excellence (NICE) Guidelines 2006, new entrant screening for those aged 16–35 from countries with an incidence of under 500/100 000 per annum was limited to a chest *x* ray only. Data presented in 2007,[1] showed that 10.5% of such individuals without treatment of LTBI developed clinical tuberculosis within 10 years. With these data we obtained funding from the Primary Care Trust (PCT), under Health Improvement initiative money, to screen those aged 16–34 age with interferon γ release assay (IGRA) testing, for a 2 year period from February 2009. Our initial experience is reported.

Methods From 1 February to date (20 July 2009) new entrant TB screening for those aged 16–34 years is by IGRA test alone