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References

Authors’ reply
We thank Dr Wildman for his letter suggesting a further possible reason for the variation in outcome that we reported for the acute care of COPD patients in different hospital centres. In a further unpublished multiple regression analysis of the RCP/BTS 2001 audit we found that 26% of the variation in the outcome of death at 90 days following admission could be accounted for by factors measured in the study that included patient characteristics such as performance status and resources and organisational issues, as described in our paper. Dr Wildman suggests that individual clinicians might vary in determining admission to the ITU for COPD patients in respiratory failure, and suggests that respiratory physicians need to be advocates for their patients in this arena.

Attitudes and beliefs in what might be achieved are important but are difficult to measure in clinical practice. They might account for some of the variation in outcome but, if so, the therapeutic nihilism would have to vary systematically between whole hospitals and not reflect a factor in our study. Admission to the ITU depends on more than just the individual attitude of the referring doctor. A lack of availability of beds may raise thresholds, and an institutional nihilism within the ITU may lead to rejection of suitable patients.

Perrin et al reported a study in which questionnaires regarding initiation of mechanical ventilation in end stage COPD patients were completed by 350 doctors subdivided by specialty (intensivists, respiratory specialists and other clinicians). As in the paper by Wildman et al, there was considerable individual variation in decision making but no overall difference between the three types of specialist studied. However, no analysis by hospital or trust was made to identify local patterns. We believe all respiratory physicians will share Dr Wildman’s call that referring physicians should be advocates for their patients, and this has to be matched by a willingness of the ITU staff to accept such patients and the availability of beds within an ITU/HDU facility to accommodate them. Perrin’s paper provides hope of a generic match although individual disagreements may still occur. It is, however, not only admission to the ITU that matters, as in many hospitals non-invasive ventilatory support is provided on general wards by respiratory units without input from intensivists. In the BTS/RCP 2003 national audit of the acute care of COPD patients, 95% of all acute admitting sites have now registered to participate and data collection is nearing completion. Within the clinical data gathering there is a question that attempts to document clinical decision making when a patient eligible for ventilation on blood gas criteria does not receive ventilatory support. In order to elicit the real need for additional, data-linked resources such as ITU beds, bed occupancy, and numbers of ITU candidates transferred off site will be recorded. We may be in a position to shed further light on the issues of individual versus institutional nihilism or rationing in due course.

Do inhaled corticosteroids slow FEV1 decline in COPD after all?
I question the findings of the meta-analysis by Sunderland et al and the content of the associated editorial by Burge and Lewis.1 The meta-analysis has drawn from available long-term data from randomised controlled studies (RCTs) of inhaled corticosteroids (ICS) in chronic obstructive airways disease (COPD). The whole purpose of meta-analysis is to synthesise such data systematically to answer a question. This study seems to use the data selectively to demonstrate an effect. Another recent meta-analysis—in my opinion properly conducted—drew on the same studies and reached the opposite conclusion.1

The fact that is four long term, adequately powered RCTs have examined the effect of ICS, all of these studies was in order of the ICS on the primary outcome measure of decline in forced expiratory volume in

References
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1 second (FEV1). There may be a subset of people in whom the exacerbation rate is reduced, which was a secondary outcome in some of these studies. In any case, as the authors point out, an annual difference of 7.7–9.9 ml in FEV1, decline compared with placebo is of “debatable clinical importance”. It is hardly something to shout about, as occurred following this publication (probably egged on by the editorial) which was quoted in the GP press as suggesting that current widespread ICS use (albeit “off-label”) was now clinically justified.

Another major problem with this study is that it does not analyse harm. For example, the largest RCT showed a significant reduction in bone mineral density of the lumbar spine and femur in patients receiving inhaled triamcinolone.4 People with COPD likely to receive ICS are frail and have poor mobility, so this finding raises particular concern as they are more likely to fall and falls could result in fracture. Even if inhaled triamcinolone is not used in the UK, fluticasone is. Fluticasone has been the subject of particular cautionary advice because of its ability to cause systemic effects at high doses.5

Hence, the editorial claimed that it is no longer ethical to do more long term trials: surely the conclusion is the opposite? We need better data to justify the widespread use of ICS in COPD.

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References

2. Burge PS, Lewis SA. Inhaled steroids slow the rate of decline of FEV1 in patients with COPD after all: Thorax 2003;58:911–3
5. CSM/MCA. Remind: Fluticasone propionate (Fluhalert) use of high doses (500 micrograms twice daily). Current Problems in Pharmacovigilance August 2001

Ethics of placebo controlled studies of inhaled steroids for COPD

The meta-analysis by Sutherland et al.1 of the effect of inhaled corticosteroids on the progression of airflow limitation in patients with chronic obstructive pulmonary disease (COPD) found a small improvement in forced expiratory volume in 1 second (FEV1) of 1.3 ml/year (95% CI 1.2 to 1.4) which was similar to the results of the meta-analysis performed by Highland et al2 (5 ml/year (95% CI 1.2 to 1.3)) using a very similar data set. The meta-analyses employed slightly different study selection criteria and analytical techniques, and questioned the clinical significance of such small differences in FEV1. The selected primary studies suffered from potential drop-out bias and significant selection bias, so this finding is similar to the results of the meta-analyses excluded patients with a bronchodilator response.3 Studies of asthma and COPD as separate entities are limited because asthma and COPD (observed in cross sections) represent a continuum,4 and the small number of available prospective observations indicates that asthma and COPD are sometimes different clinical manifestations of the same underlying aetiology evolving over time.5

Given all the uncertainties, questions and limitations, Highland et al6 concluded (correctly in my opinion) that “additional studies are needed to evaluate the effects on quality of life, risk for systemic side effects, dose-response relationships in corticosteroid-responsive patients, and the economic efficacy of inhaled corticosteroids”. On the other hand, in an editorial accompanying the paper by Sutherland et al, Burge and Lewis7 state: “It is no longer ethical to do more long term placebo controlled studies of [inhaled corticosteroids in COPD].” Given the uncertainties, questions and limitations which Burge and Lewis acknowledged, I was puzzled by this statement and would like to ask them why they reached this conclusion.

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Authors’ reply

To make randomised controlled studies ethical, the investigator must believe that neither treatment is known to be superior to the other. If the trial is to be placebo controlled, the investigators must believe that no non-allowed treatment is known to be of benefit. Both Drs Duerden and Hahn want more placebo controlled trials of inhaled corticosteroids (ICS) in COPD before they recommend their routine use. In my opinion this is indeed a marginal clinical benefit from inhaled triamcinolone.6–10 So this finding raises particular concern because of its ability to cause systemic effects at high doses.11, 12

I think these people deserve a better assessment of risk and benefit than was presented in this meta-analysis and the accompanying editorial.13 The editorial claimed that it is no longer ethical to do more long term trials: surely the conclusion is the opposite? We need better data to justify the widespread use of ICS in COPD.

There are 11 references cited in the text. They are listed below for easy access.

2. Burge PS, Lewis SA. Inhaled steroids slow the rate of decline of FEV1 in patients with COPD after all: Thorax 2003;58:911–3
5. CSM/MCA. Remind: Fluticasone propionate (Fluhalert) use of high doses (500 micrograms twice daily). Current Problems in Pharmacovigilance August 2001

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unanswered questions are—at which stage to start and what dose to use? Randomised trials in these areas are badly needed. They will require large numbers, enthusiasm from respiratory clinicians, and are likely to need public rather than pharmaceutical industry funding.

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References
1 Burge PS, Lewis SA. So inhaled steroids slow the rate of decline of FEV1 in patients with COPD after 8 years (range 0.5–62) and 133 patients 84.3% of respondents excessive daytime difficulties in defining disease and the lack of this had been made a median of 12 years compared with healthy controls.3 In addition to the health and quality of life benefits to the individual to be gained by prompt diagnosis, there are also economic aspects in favour of prompt diagnosis and treatment and early benefits in terms of driving performance.7

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Delay in diagnosis of OSASH
We very much enjoyed the first paper in the series on sleep and administered Strugling and Davies’s honest appraisal of the current difficulties in defining disease and the lack of a relationship between symptoms and the results of investigations. One of the problems of truly determining the size of the health burden associated with the obstructive sleep apnoea/hypopnoea syndrome (OSASH) is that much of the burden may occur before the diagnosis is made. Others have shown how important hospital resources and use of cardiovascular medication is high in those with undiagnosed obstructive sleep apnoea.7,8 We administered a questionnaire to 166 consecutive patients with diagnosed OSASH on continuous positive airway pressure treatment and asked them to identify how long they could recall having symptoms at the time of diagnosis. In 155 cases (93.4%) someone had previously complained of the patient’s loud snoring and first mention of this had been made of a median of 12 years (range 2–52) before diagnosis of OSASH. In 84.3% of respondents excessive daytime sleepiness had been present for a median of 8 years (range 0.5–62) and 133 patients (80.1%) reported that their bed partner had witnessed apnoea a median of 8 years (range 1–49) before diagnosis. We also found that, of the 119 (71.7%) who were drivers, 26 (21.8%) reported at least one or more automobile crashes in the previous 5 years, with seven respondents having had two and one having had four.

These results suggest a lack of awareness of sleep related breathing disorders among the general population and probably among health professionals. The delay in diagnosis is likely to have significant effects on morbidity, and in recent preliminary work it has been shown that those with OSASH have structural changes in brain morphology compared with healthy controls. In addition to the health and quality of life benefits to the individual to be gained by prompt diagnosis, there are also economic aspects in favour of prompt diagnosis and treatment and early benefits in terms of driving performance.7

Prophylactic antibiotic treatment of bronchiectasis with azithromycin
Once a treatable cause of bronchiectasis such as hypergammaglobulinaemia has been excluded, management largely involves physiotherapy and treatment of infective exacerbations with appropriate antibiotics.1 In a proportion of patients this is not adequate to prevent frequent infective exacerbations. Prophylactic antibiotic treatment can be used to try to prolong the exacerbation free period. This may be administered orally, via a nebuliser, or possibly as a regimen of intravenous antibiotics. Prophylactic treatment may be problematic due to side effects and development of antibiotic resistance.2 Macrolide antibiotics exhibit immunomodulating properties. Long term low dose erythromycin has been shown in diffuse panbronchiolitis, a disease with some similarities to idiopathic bronchiectasis, to be effective in controlling chronic supplicative airways disease.4 Recently published research has shown benefits of long term azithromycin treatment in patients with bronchiectasis.5,6 These results led us to consider using azithromycin as prophylaxis in patients with non-cystic fibrosis bronchiectasis with frequent infective exacerbations.

Exclusions included allergy to macrolides and abnormal liver function tests. The single dose was 500 mg once daily for 6 days, 250 mg once daily for 6 days, then 250 mg on Monday/Wednesday/Friday of each week. A safety blood examination was organised 1 month after starting treatment. The patients were fully reviewed at least 4 months after commencement of azithromycin prophylaxis and lung function tests repeated. Sputum culture results before and after starting prophylaxis were noted. Statistical analysis was performed using a paired t test and non-parametric Wilcoxon test.

Thirty nine patients were studied. Fifteen had idiopathic bronchiectasis and the remainder consisted of 13 with post childhood infections, five with primary ciliary dyskinesia, five with common variable immunodeficiency, and one with Young’s syndrome. Their mean (SD) age was 51.9 (16.1) years (range 18–77) with a 2:1 female predominance. All patients had had more than four documented exacerbations during the previous 12 months. Six patients stopped taking the azithromycin prophylaxis after 6 months due to side effects: abnormal liver function tests (n = 2), diarrhoea (n = 2), rash (n = 1), and tinnitus (n = 1). All occurred during the first month of treatment. Other side effects experienced were mild and mainly gastrointestinal. Five patients were on long term oral corticosteroids with no change in dosage, in two new inhaled corticosteroids were introduced, and one patient was given a short 1 day course of short and long acting oral corticosteroids. The mean (SD) length of time taking azithromycin, excluding those who stopped because of side effects, was 20 (10.1) months (range 4–38). Twenty six patients are continuing with the prophylaxis at the present time; in the other seven treatment was discontinued because of improvement in their condition.

Sputum culture results (bacteria isolated) before commencement showed no growth (n = 13), Pseudomonas aeruginosa (n = 8), Staphylococcus aureus (n = 6), Haemophilus influenzae (n = 6), Streptococcus pneumoniae (n = 3), Stenotrophomonas maltophilia (n = 2), Morexella catarrhalis (n = 1), not done (n = 4). After 4 months the results were no growth (n = 18), P aeruginosa (n = 5),
S aureus (n = 1), S pneumoniae (n = 1), not done (n = 10). In three patients who had cultured P aeruginosa before starting azithromycin prophylaxis the organism was not recultured at follow up.

In the 33 patients completing at least 4 months treatment there was a statistically significant reduction in infective exacerbations requiring oral antibiotics from a mean of 0.71 per month to 0.13 per month (p<0.001). There was also a reduction in the requirement for intravenous antibiotics from a mean of 0.08 courses per month to 0.003 courses per month (p<0.001). Subgroup analysis of patients with P aeruginosa isolated before starting azithromycin prophylaxis showed no difference compared with all patients included (p = 0.22). Twenty five patients had lung function tests before and after at least 4 months of treatment (range 4–20 months). There was an improvement in all lung function parameters but the improvement in carbon monoxide transfer factor (TLC0) was the only one to reach statistical significance (p = 0.01).

Symptom data were collected from 32 patients and scored on a 5-point scale (table 1). Statistical analysis using a non-parametric Wilcoxon test showed that there was a significant improvement in all symptoms.

The mechanism by which azithromycin reduces the number of infective exacerbations and chronic symptoms is unknown, but it is likely to be multifactorial. It may be due to downregulation of the host immune response by azithromycin, so decreasing host mediated tissue damage as postulated in the vicious circle hypothesis. It might also benefit patients by reducing bacterial load and therefore the stimulation for neutrophilic inflammation, or by influencing the pathogenic mechanisms of bacteria. Macrolide antibiotics have also been shown to reduce mucus secretion.

Currie et al compared high dosage amoxycillin with placebo over an 8 month period and found a greater reduction in the volume of purulent sputum between exacerbations in the amoxicillin group (to 20% of pretreatment volume) than in the placebo group, but did not demonstrate any reduction in infective exacerbations. The superior findings of our study suggest that the anti-inflammatory effects of azithromycin were important in achieving the results obtained. This study was performed with patients who were sufficiently unwell to preclude consideration of a placebo group. The patients therefore acted as their own controls. The results are sufficiently impressive to encourage the design of a randomised study, either enrolling less sick patients and having a placebo comparator or using a comparator antibiotic without immunomodulating properties.

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Table 1 Change in symptoms while taking azithromycin prophylaxis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum volume</td>
<td>1.6</td>
<td>0.8</td>
<td>0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sputum colour</td>
<td>2.1</td>
<td>0.7</td>
<td>0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sputum consistency</td>
<td>2.5</td>
<td>0.6</td>
<td>0.11</td>
<td>0.006</td>
</tr>
<tr>
<td>Cough</td>
<td>2.4</td>
<td>0.7</td>
<td>0.12</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.1</td>
<td>1.0</td>
<td>0.18</td>
<td>0.001</td>
</tr>
<tr>
<td>Exercise tolerance</td>
<td>3.8</td>
<td>0.9</td>
<td>0.16</td>
<td>0.002</td>
</tr>
<tr>
<td>Wheeze</td>
<td>2.6</td>
<td>0.8</td>
<td>0.14</td>
<td>0.011</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>2.3</td>
<td>0.7</td>
<td>0.13</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Symptoms scored on a 5-point scale: 1 = large decrease, 2 = decrease, 3 = no change, 4 = increase, 5 = large increase in symptoms.

Cullinan et al present interesting data on the association between exposure to antibiotics in early life and the subsequent expression of atopy and asthma. In keeping with other studies, they report a positive association between antibiotic receipt over the first 5 years of life and asthma. The association was, however, largely accounted for by prescriptions issued for respiratory illnesses, and the authors conclude that reverse causation was the likely explanation for this association.

The inappropriate use of antibiotics for respiratory symptoms caused by unrecognised asthma is the main potential confounding factor in observational studies attempting to demonstrate a causal link between antibiotic receipt and atopic illnesses. It is certainly plausible that GPs may prescribe antibiotics in children with symptoms such as cough and wheeze in early life. Suggestions of a causal link between antibiotic exposure to asthma cannot be made from our study. Farooqui and Hopkins did, indeed, observe an association with non-respiratory use of antibiotics and asthma; in the study by Cullinan et al the association between non-respiratory indicated antibiotics and atopic asthma narrowly failed to reach statistical significance. The authors acknowledge that the study was only powered to show a doubling of the odds ratio for the association between early life antibiotic use and asthma, so an association remains possible in this cohort.

The most important limitation of the study, however, is the timing of the observed early life events in relation to secular changes in asthma prevalence and antibiotic prescribing, and hence the applicability of the results to modern day settings. This study observed events occurring 30 or more years ago in the parents of the Ashford birth cohort. As is well described, the prevalence of asthma has increased greatly over the last 30 years. There may also have been significant increases in antibiotic prescribing over this time. The subjects in this study received an average of 3.1 and a median of 5 antibiotic prescriptions over 5 years, while we found in a recent case-control study of 37 children with atopy and wheezing and 37 without either that the average and median number of antibiotic courses received during the first 5 years of life was 9.9 and 7 and for wheezers 6.3 and 5 for non-wheezers. There is also evidence of earlier prescribing of antibiotics in recent times; in our study group 89% of wheezers and 68% of non-wheezers received one or more courses of antibiotics in the first year, while in the Ashford study only 396 prescriptions were issued to 746 subjects in the first year, so a maximum of 53% children received any antibiotics.

It seems likely from the data presented that antibiotic exposure did not play a major causal role in promoting the asthma phenotype 30 years ago when both the prevalence of asthma and antibiotic prescribing to young children were significantly less than they are now, but the question of whether it may now be a significant and potentially modifiable factor remains unanswered.

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References

Early life antibiotics and asthma

Cullinan et al were the first to present evidence on the association between exposure to antibiotics in early life and the subsequent expression of atopy and asthma. In keeping with other studies, they report a positive association between antibiotic receipt over the first 5 years of life and asthma. The association was, however, largely accounted for by prescriptions issued for respiratory illnesses, and the authors conclude that reverse causation was the likely explanation for this association.

The inappropriate use of antibiotics for respiratory symptoms caused by unrecognised asthma is the main potential confounding factor in observational studies attempting to demonstrate a causal link between antibiotic receipt and atopic illnesses. It is certainly plausible that GPs may prescribe antibiotics in children with symptoms such as cough and wheeze in early life. Suggestions of a causal link are strengthened by demonstration of an association when antibiotics were used for symptoms not associated with asthma. The earlier study by Farooqui and Hopkins did, indeed, observe an association with non-respiratory use of antibiotics and asthma; in the study by Cullinan et al the association between non-respiratory indicated antibiotics and atopic asthma narrowly failed to reach statistical significance. The authors acknowledge that the study was only powered to show a doubling of the odds ratio for the association between early life antibiotic use and asthma, so an association remains possible in this cohort.

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Recurrence of acute respiratory failure following use of waterproofing sprays

Between January and March 2003 six patients were admitted to hospital in the Lausanne area of Switzerland with acute respiratory failure following use of a waterproofing spray for clothes and leather. Within hours of exposure all patients developed a dry cough and rapidly progressed to respiratory failure. The clinical picture included severe hypoxaemia, increased white blood cell count, raised C-reactive protein, and reduced carbon monoxide
transfer factor (TLC0). All patients had diffuse bilateral ground glass opacities on a high resolution CT scan, most often sparing the subpleural areas (fig 1). Every patient improved following treatment with oral prednisone (0.5–0.9 mg/kg) but residual dyspnoea and reduced TLC0 (<80% of predicted value) could be seen for more than 2 weeks.

Acute respiratory failure was attributed to inhalation of the waterproofing spray in view of the sudden occurrence of symptoms following exposure, the diffuse ground glass opacities without other abnormalities on the CT scan, and the absence of any other detected cause. In particular, BAL fluid was sterile for bacteria, mycobacteria, viruses and fungi. Serological tests for chlamydia and mycoplasma were performed on two patients and were negative. A nasal swab for influenza was performed on one patient and was negative.

We were, however, surprised that the patients used three different spray brands. Waterproofing sprays contain three types of components—a propellant gas (propane butane), a waterproofing agent (fluorocarbon resin), and a solvent. It appeared that the manufacturer of the fluorinated resin changed during the summer of 2002 (the same for the three brands) and that the isopropyl alcohol had to be replaced with a heptane solvent. Consumers started complaining of respiratory symptoms in October 2002 and the first severe case requiring admission was reported in January 2003. The three products were withdrawn from the market at the beginning of March. During this 6 month period 153 cases of respiratory symptoms related to waterproofing sprays were reported to the Swiss Toxicological Information Centre, whereas less than 10 cases per year had been reported in the previous 7 years. The same fluorinated resin was also distributed in Germany, the Netherlands, and the UK. In Germany the spraying sprays were withdrawn before they reached the consumers. During the same period five patients were admitted to hospital in the Netherlands with the same complaints.

These sprays were also withdrawn from the Dutch market. Surprisingly, no case has yet been recorded in the UK.

However, only sprays for public use were withdrawn, not the industrial liquids. In Switzerland two additional patients developed a chemical pneumonitis with similar symptoms of diffuse bilateral ground glass opacities after using industrial waterproofing liquid with a nebuliser. Workers in the above mentioned countries should therefore be warned not to use the liquid form with nebulisers.

In the past, several outbreaks of acute respiratory symptoms have been recorded in different countries including 550 in Oregon in 1992,\(^1\) in Pennsylvania and Virginia in 1993,\(^2\) in Quebec in 1993,\(^3\) and in Japan between 1992 and 1993.\(^4\) Most of these epidemics followed publication of the composition of the spray. One untreated patient developed a pulmonary fibrosis during a German outbreak in the 1980s\(^2\) and one death was reported in Japan in the 1990s.\(^4\)

Following these outbreaks various suggestions were proposed to explain these intoxications.\(^5\) In our opinion, the most likely explanation for the present outbreak is that the heptane solvent, which is more volatile than the previous one (isopropanol), allows the mist containing the new fluorinated resin to spread further in the tracheobronchial tree and to reach the alveoli where it might produce reactive metabolites inducing an alveolitis. However, the exact chemical reaction remains unknown. Because of the potentially lethal aspect of these intoxications and the possibility of new outbreaks, we consider that more research is needed on the effect of mist particle size and large analytical epidemiological studies are required to investigate this phenomenon further.

References


Effect of PM10 on H influenzae and S pneumoniae

That air pollution, and specifically particles, are harmful to health is well accepted,\(^1\) causing direct effects such as lung inflammation resulting in exacerbations of lung and cardiac conditions\(^2\) and being associated with admissions for preexisting conditions. In the 1960s Lawther et al showed that ambient particles stimulated the growth of Haemophilus influenzae in vitro,\(^3\) suggesting a direct effect of particles on bacteria themselves. However, it is not known whether this remains so for modern ambient particles where the sources are different.

To address this we have assessed the effect of PM10 (particles essentially less than 10 μm in diameter) on the respiratory pathogens commonly associated with acute exacerbations of chronic obstructive pulmonary disease (COPD) and pneumonia. The effect of dilutions of extracts of PM10 on the growth of H influenzae and Streptococcus pneumoniae grown in liquid broth and the effect of PM10 on microbial growth kinetics of S pneumoniae was assessed.

Fresh isolates of H influenzae and S pneumoniae obtained from clinical specimens and the control strains H influenzae NCTC 11931 and S pneumoniae ATCC 49619 were used. Particles were collected on a tapered element oscillating microbalance situated in central Birmingham, representative of urban background site. To obtain a usable sample the surface of the filter was wetted and rinsed with two sequential aliquots of 0.5 ml saline using a Gilson pipette until visual inspection showed no more particles coming off the filter. The two aliquots were combined and sonicated for 2 minutes to disperse the particles and aggregates. This procedure usually gives a yield of 50–300 μg/ml particles (Donaldson, personal communication). It is not known for certain how these concentrations relate to likely concentrations in the epithelial lining fluid, but this approach has been used in previous in vitro studies of inflammatory responses which have shown pro-inflammatory effects.

In the first experiment a 1:20 dilution of PM10 was made by adding 0.5 ml to 9.5 ml iso sensitiser broth (ISTA; Oxoid Ltd, Basildon, UK) supplemented with 5% lysed horse blood and 20 μg/ml NAD. The same volume of normal saline was added to controls. Test and control bottles were inoculated with 0.5 ml of organism suspension at a density of 0.5 McFarland. A viable count was performed hourly for 5 hours while incubating at 37°C in 5% CO2 using the Miles and Misra technique.\(^4\) In the growth kinetic experiment equal volumes of PM10 solution and ISTA broth (supplemented with 5% lysed horse blood and 20 μg/ml NAD) were added to the first column of a sterile microtitre tray. Serial broth dilutions to a final dilution of 1:16 were performed from control wells containing only broth and wells for sterility checks contained PM10 alone, broth alone and inoculum alone. Organism suspension, 50 μl S pneumoniae ATCC 49619, was added to each test and control column of the wells and incubated at 37°C in 5% CO2 for 5 hours. The Miles and Misra technique\(^5\) was used to estimate the viable count of organism in each well and the differences in log cfu/ml between test and control were plotted against serial dilutions of PM10. This test was repeated five times using the same strain to check for reproducibility.

In the first experiment the number of viable cells increased progressively and in the expected pattern over time (fig 1A and B), whether in the presence or absence of PM$_{10}$, for both H influenzae and S pneumoniae. In the growth kinetics experiment the only consistent finding was an inhibition of growth at a PM$_{10}$:broth medium dilution of 1:1, possibly due to the particles themselves or to dilution of the broth by the added saline. These findings suggest that the association of air pollution with hospital admissions for exacerbations of COPD and for pneumonia is probably not mediated through direct promotion of bacterial growth. If particles alone are responsible for these effects, they are likely to be mediated by particles causing lung inflammation, thus encouraging penetration and growth of bacteria in the respiratory tract. Alternatively, gaseous pollutants may be responsible for the epidemiological findings, either directly or in conjunction with particles. This interactive mechanism is supported by the association of ambient nitrogen dioxide levels with admissions for croup, and is analogous to the potentiation of the airway response to inhaled allergen by both nitrogen dioxide and ozone. Finally, it is possible that the particles have an effect on bacterial virulence and toxin production rather than growth. This possibility has not been tested here but warrants further study.

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CORRECTIONS

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PAPER BY BALDI ET AL (THORAX 2004;59:428-32)
In the paper entitled “Prognostic significance of cyclooxygenase-2 (COX-2) and expression of cell cycle inhibitors p21 and p27 in human pleural malignant mesothelioma” by A Baldi, D Santini, F Vasaturo, et al published in the May 2004 issue of Thorax (2004;59:428-32) there was an error in the sentence beginning on line 14 of the left hand column on page 430. The sentence should have read “The median survival in patients with low p21 or p27 expression was shorter than in those with high p21 or p27 expression.” The publishers apologise for this error.

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