Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of *Mycobacterium vaccae* immunotherapy

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ABSTRACT

Background: The mainstays of treatment for pulmonary disease caused by opportunist mycobacteria are rifampicin (R) and ethambutol (E). The role of macrolides, quinolones and immunotherapy with *Mycobacterium vaccae* is not clear. A trial was undertaken to compare clarithromycin (Clari) and ciprofloxacin (Cipro) as third drugs added after 2 years of treatment with R and E for pulmonary disease caused by *M avium-intracellulare* (MAC), *M malmoense* and *M xenopi* (REClari and RECipro). An optional comparison of immunotherapy with *M vaccae* vs no immunotherapy was also performed.

Methods: Progress was monitored annually during the 2 years of treatment and for 3 years thereafter. If the patient was not improving at 1 year the regimen was supplemented by the addition of the drug not received in the original allocation of treatment.

Results: 371 patients (186 REClari, 185 RECipro) entered the study (170 MAC, 167 *M malmoense*, 34 *M xenopi*). All-cause mortality was high for both groups (44% REClari, 43% RECipro); for MAC it was higher with REClari than with RECipro (48% vs 29%) but for *M malmoense* (42% vs 56%) and *M xenopi* (29% vs 47%) it was higher with RECipro (p = 0.006). 3% died from their mycobacterial disease (REClari = RECipro). At the end of treatment, 4% of REClari and 10% of RECipro patients still had positive cultures. Among those with negative cultures at the end of treatment, 6% of the REClari group and 4% of the RECipro group had relapsed. At 5 years 30% of the REClari group were known to have completed treatment as allocated and to be alive and cured compared with 21% of the RECipro group (p = 0.04), but this difference was principally due to those with *M malmoense* (REClari 38%, RECipro 20%). Patients with MAC or *M xenopi* were more likely to have a poor outcome than those with *M malmoense* (p = 0.004), with no difference between REClari and RECipro. Overall, 20% in each group were unable to tolerate the regimen allocated, Cipro being associated with more unwanted effects than Clari (16% vs 9%, p = 0.05). No significant differences in outcomes were found between *M vaccae*-treated patients and those not treated with *M vaccae* immunotherapy.

Conclusion: Considering all three species together, there were no differences in outcome between the REClari and RECipro groups. Immunotherapy did not improve outcome. New therapies, optimised management of co-morbid conditions and a more holistic approach must be explored in the hope of improving outcome.

In 2001 the Research Committee of the British Thoracic Society (BTS) published the results of the first prospective randomised trial of treatments for pulmonary disease caused by the opportunist mycobacteria *Mycobacterium avium intracellulare scrofulaceum* (MAC or MAIS), *M malmoense* and *M xenopi*. That trial showed that 2 years of treatment with rifampicin (R) and ethambutol (E) or with R+E+isoniazid (H) achieved results comparable with those reported with previous regimens, which often contained five or six antimycobacterial drugs, but with considerably fewer problems from drug intolerance.[1] The REH regimen reduced failure/relapse rates more than RE but was associated with an increased death rate from the mycobacterial disease. While the trial was in progress the macrolide and quinolone agents clarithromycin (Clari) and ciprofloxacin (Cipro) were shown to have in vitro activity against opportunist mycobacteria.[2 3] There had been reports of their efficacy in vivo,[2 4–8] but randomised clinical trials which demonstrated efficacy had only been reported for MAC in HIV positive patients.[9–11] The Research Committee of the BTS has conducted a further multicentre, prospective, randomised, international, open-label pragmatic trial to assess the values of Clari and of Cipro in the treatment of opportunist mycobacterial pulmonary disease in patients who were not known to be HIV positive: REClari for 2 years vs RECipro for 2 years. In addition, because of evidence emerging at the time,[12 13] there was an option in the trial where patients could be further randomised to receive immunotherapy with *M vaccae* (SRL 172)[12] or to receive no immunotherapy.

METHODS

Patients

Patients were eligible for inclusion in the study if (1) they were aged ≥16 years; (2) they had clinical and/or radiological evidence of active mycobacterial disease; (3) sputum was positive on culture for MAC, *M malmoense* or *M xenopi* on at least two occasions a minimum of a week apart; (4) they were not known to be HIV positive; and (5) they gave informed consent.

Pregnant women and women of childbearing age not taking adequate contraceptive precautions and patients who had sputum currently positive on culture for *M tuberculosis* or *M bovis* were not included in the study. HIV tests were not requested but patients known to be HIV positive were excluded from the study.

The Regional Centres for Tuberculosis (TB) Bacteriology in Cardiff, Birmingham and Newcastle, the Mycobacterium Reference Unit (MRU) Dulwich and the Scottish Mycobacterium Reference Laboratory, City Hospital, Edinburgh informed the coordinator of the trial when two positive isolates were obtained from a patient. The coordinator contacted the patient's physician and informed him/her of the trial. Once the physician and patient agreed to enter the trial, treatment was allocated centrally by the coordinator from separate randomisation lists based on randomised permuted blocks for each of the three species. Scandinavian and Italian physicians contacted the coordinator directly, as did the occasional physician in Britain. A factorial design was used for patients agreeing to enter the immunotherapy limb of the trial so that, for these patients, there were four possible treatments:

► RECipro
► RECipro + *M vaccae* 4 times in first 6 months
► REClari
► REClari + *M vaccae* 4 times in first 6 months

Patients choosing not to enter the immunotherapy limb of the trial were randomised between RECipro and REClari.

The physician was asked to discontinue any antimycobacterial drugs other than those to which the patient had been allocated and to complete and return an entry form giving details of the patient's age, sex, weight, BCG status, previous pulmonary disease(s) and date of start of treatment with the trial regimen. On that form the physician also confirmed the dosages of the trial drugs as follows:

► Rifampicin: 450 mg (or 600 mg in those weighing 50 kg or more) orally once daily.
► Ethambutol: 15 mg per kg orally once daily.
► Clarithromycin: 500 mg twice daily.
► Ciprofloxacin: 750 mg twice daily.
► *M vaccae* 0.1 ml intradermally on entry and every 2 months up to 6 months (ie, four doses in all).

Patients weighing less than 50 kg were asked to take their tablets on an empty stomach. Decisions about inpatient or outpatient management were left to the physician and the protocol did not request directly observed therapy.

The pretreatment chest radiograph was sent to the coordinator with the entry form. This was read by the coordinating physician using a standard method of grading extent of disease and cavitation who was unaware of the regimen the patient had received.[1]

During chemotherapy the physician was asked, for purposes of the trial, to review the patient at 12 and 24 months, recording clinical progress, weight, tolerance to chemotherapy and confirmation of its prescription on forms sent by the coordinator. If the sputum at 12 months proved positive on culture, the Regional/National Laboratory notified the coordinator and the patient's physician who was then required to add the fourth drug (Cipro to those on REClari or Clari to those on RECipro). A reminder to discontinue chemotherapy was sent with the review form at 24 months. Patients whose sputum was still positive on culture on two occasions, separated by an interval of at least 2 weeks in the last 3 months of treatment, were classed as treatment failures. Patients who, despite treatment, deteriorated as a result of their mycobacterial disease and whose chemotherapy was therefore altered from that allocated were also classed as treatment failures.

After the patient had completed chemotherapy, the physician was asked to report, by means of pre-sent review forms, the clinical and bacteriological status (two specimens of sputum) every 12 months for a further 3 years (ie, up to 5 years from

entry to the trial). Those whose sputum became positive on culture (two specimens separated by at least 2 weeks) were classed as relapses. Further treatment was left to the discretion of the physician.

If the patient died during the study the cause of death was ascertained from the physician and/or general practitioner (GP) and/or a report of the post mortem examination. Using these data, deaths were classified by the coordinating physician as being caused either by opportunist mycobacterial pulmonary disease or not being so caused, and were analysed as "all cause" mortality and as mortality directly attributed to the mycobacterial disease.

Statistical analysis

The statistical methods applied are all standard. The analysis, based on intention-to-treat, was undertaken using SPSS Version 13 and SAS Version 9.1. There were no formal power calculations undertaken before the commencement of the trial. It was regarded as a study to estimate the magnitude of differences between the treatment arms with as much precision as numbers permitted over the period of the trial. Recruitment took place over 5 years and the decision to stop recruiting was made independently of efficacy data as a compromise between maximising trial input and financial constraints. Primary end points for analysis were (1) death due to mycobacterial disease; (2) failure of treatment; and (3) relapse. Secondary end points were (1) all-cause mortality; (2) unwanted effects of chemotherapy and/or immunotherapy; (3) a combination of the primary end points into a composite measure of "poor outcome"; (4) a composite measure of "good outcome" defined as completing treatment as allocated and alive and cured at the end of 5 years; (5) clinical progress as recorded over the follow-up points during the trial; and (6) number of patients requiring addition of the fourth drug and outcome in those patients.

RESULTS
Recruitment and randomisation
Between March 1995 and September 1999, 191 physicians from England, Scotland, Wales, Denmark, Finland, Norway, Sweden and Italy entered 386 patients, of whom 15 did not fulfil the criteria for eligibility for the trial, leaving 371 patients for analysis (MAC 170; *M malmoense* 167; *M xenopi* 34). Of these, 201 opted not to enter the immunotherapy randomisation and were randomised just between REClari and RECipro (table 1). The remaining 170 patients chose to enter the immunotherapy limb and were randomised between REClari and RECipro as well as between *M vaccae* and no *M vaccae*, 84 patients receiving *M vaccae* and chemotherapy while 86 received chemotherapy but no *M vaccae* (table 2).

In the 201 patients who elected not to enter the immunotherapy limb, the REClari and the RECipro groups were not appreciably different in mean age, previous BCG vaccination, radiological extent of disease, cavitation and evidence of other pulmonary disease on the chest radiograph, although a higher proportion of men were randomised to REClari (table 1). The distributions for patients randomised to immunotherapy (n = 84) or no immunotherapy (n = 86) were similar except for an excess of patients in the immunotherapy arm with BCG vaccination and an excess with cavitation (table 2). Within the subgroups randomised for immunotherapy, the REClari group had a higher proportion of patients with BCG vaccination and women. In the trial population as a whole, the distributions were similar for REClari and RECipro.

Table 1 Pretreatment characteristics of patients not opting for the immunotherapy limb of the study

	MAC		M malmoense		M xenopi		All 3 species	
	REClari (n = 47)	**RECipro (n = 50)**	**REClari (n = 43)**	**RECipro (n = 40)**	**REClari (n = 11)**	**RECipro (n = 10)**	**REClari (n = 101)**	**RECipro (n = 100)**
Sex (M/F)	25/22	20/30	30/13	24/16	10/1	7/3	65/36	51/49
Mean (SD) age (years)	67.3 (11.6)	64.6 (12.5)	62.7 (11.4)	62.7 (12.3)	61.7 (11.1)	62.8 (10.3)	64.7 (11.6)	63.7 (12.1)
BCG vaccination	7 (15%)	9 (18%)	3 (7%)	6 (15%)	3 (27%)	1 (10%)	13 (13%)	16 (16%)
Cavitation	33 (70%)	32 (64%)	17 (40%)	18 (45%)	9 (82%)	8 (80%)	59 (58%)	58 (58%)
≥3 zones	8 (17%)	5 (10%)	9 (21%)	5 (13%)	1 (9%)	3 (30%)	18 (18%)	13 (13%)
Other pulmonary disease on chest radiograph	29 (62%)	26 (52%)	8 (19%)	16 (40%)	8 (73%)	8 (80%)	45 (45%)	50 (50%)

Cipro, ciprofloxacin; Clari, clarithromycin; E, ethambutol; MAC, *Mycobacterium avium intracellulare*; R, rifampicin.

Deviations from protocol

In 140 patients the protocol was not followed: 75 (20.2%) experienced unwanted effects necessitating a change of the regimen (38 (20.5%) RE Cipro and 37 (19.9%) REClari). Of these, 54 received treatment different from that allocated because of unwanted effects definitely caused by a single drug: R, 9 (2.4%); E, 20 (5.4%); Cipro, 17 (9.2%); Clari, 8 (4.3%). A further 17 patients were intolerant to each (definitely or possibly) of the three drugs in their regimen (9 RECipro, 8 REClari), while 4 other patients (all RECipro) were intolerant of two (definitely or possibly) of their three drugs. Overall, Clari was associated with unwanted effects in 16 (8.6%) and Cipro was associated with unwanted effects in 29 (15.6%) (difference −7.1% (95% CI −13.7% to −0.5%, p = 0.05). The corresponding figures for R were 12 (6.5%) and 15 (8.1%), p = 0.68. Among the REClari group there were 25 (13.4%) with unwanted effects attributed to ethambutol compared with 16 (8.6%) in the RECipro group (difference 4.8%, 95% CI −1.6% to 11.2%, p = 0.19). Within these, visual problems predominated in the REClari group (n = 15 (8.1%) vs 5 (2.7%) in the RECipro group; difference 5.4%, 95% CI 0.8% to 9.9% p = 0.04). However, on retrospective enquiry after the end of the trial, it was discovered that in at least 4 of the 15 REClari patients and in 1 of the 5 RECipro patients the visual problems had been attributed incorrectly to ethambutol, altering the comparison to 11 REClari vs 4 RECipro 4 (difference 3.8%, 95% CI −0.2% to 7.7%, p = 0.12).

In a further 62 patients, treatment varied from that allocated because of physicians' errors, general practitioners' errors, other medical/surgical problems (none were HIV/AIDS) or patients' non-compliance with treatment or follow-up. In all of these respects there were no differences between the REClari and RECipro groups, nor were there any differences between the groups randomised to *M vaccae* or to no *M vaccae*. In addition, three patients randomised to REClari were unable to tolerate Cipro when added as a fourth drug.

Immunotherapy

Considering the 170 patients who participated in the immunotherapy limb of the trial (table 3), no significant differences were found within species nor overall between those receiving *M vaccae* and those not in terms of total deaths (*M vaccae* 36 (42.9%), no *M vaccae* 38 (44.2%)), deaths due to opportunist mycobacterial disease (*M vaccae* 5 (6%), no *M vaccae* 2 (2.3%)), failure of treatment (*M vaccae* 6 (7.1%), no *M vaccae* 3 (3.5%)) and relapses (*M vaccae* 2 (2.4%), no *M vaccae* 4 (4.7%)). A poor outcome of treatment (death due to opportunist mycobacterial disease or failure of treatment or relapse) was experienced by 13

(15.5%) in the *M vaccae* group and 8 (9.3%) in the no *M vaccae* group (difference 6.2%, 95% CI −3.7%, 16.0%, p = 0.32). For purposes of the comparison of REClari with RECipro, these 170 patients were combined with the 201 who had opted not to enter the immunotherapy limb, giving totals for analysis of 186 in the REClari group and 185 in the RECipro group.

Comparisons of the chemotherapy regimens (n = 371)
Deaths

Within each species and overall, the number of patients who died because of mycobacterial disease did not differ between the REClari and RECipro treatment groups (REClari 6 (3.2%) vs RECipro 6 (3.2%; table 4).

In the total trial population there was no difference in all-cause mortality between the REClari and RECipro regimens (Mantel-Haenszel χ^2 <0.001, p = 0.99), but there was significant heterogeneity in the magnitude of the treatment effect across the three species (p = 0.006, Breslow-Day test of homogeneity of odds ratios; table 4). Among the patients with MAC the mortality was higher in the Clari arm than in the Cipro arm (48% vs 29%), while this was reversed for patients with *M malmoense* (42% vs 56%) and *M xenopi* (29% vs 47%).

Of the 148 patients who died from causes other than mycobacterial disease, 58 died of respiratory failure, 17 of lung cancer, 2 of pneumonia, 1 of pneumothorax, 1 of cor pulmonale, 1 of pulmonary embolism, 28 of other cardiovascular diseases, 14 of non-respiratory malignancy and 9 of other causes (none due to AIDS or drug toxicity). In relation to these various causes of death, there were no differences between the REClari and RECipro regimens. In 17 patients (9 REClari, 8 RECipro) the cause of death was uncertain.

Failures of treatment and relapses

In the REClari group, 19 (10.2%) either failed treatment (n = 7) or relapsed after the end of treatment (n = 12) compared with 25 (13.5%) in the RECipro group (18 failures of treatment and 7 relapses) (difference −3.3%, 95% CI −9.9% to 3.3%, p = 0.41; table 4).

Poor outcome

Combining deaths due to mycobacterial disease with failures of treatment and relapses to generate the index ''poor outcome'', there was no evidence of an overall treatment effect of REClari versus RECipro (Mantel-Haenszel χ^2 = 0.72, p = 0.40), nor was there evidence of different treatment effects in the three species (p = 0.30, Breslow-Day test). Poor outcome rates did differ between the species (MAC 19%; *M xenopi* 18%; *M malmoense* 7%: χ^2 = 11.1, p = 0.004). The overall poor outcome rate of

Table 2 Pretreatment characteristics of patients entering the immunotherapy limb of the study

| | M avium intracellulare RE | | | | M malmoense RE | | | | M xenopi RE | | | | All 3 species | | | |
| | M vaccae | | No M vaccae | | M vaccae | | No M vaccae | | M vaccae | | No M vaccae | | M vaccae | | No M vaccae | |
	Clari (n = 17)	Cipro (n = 19)	Clari (n = 19)	Cipro (n = 18)	Clari (n = 21)	Cipro (n = 21)	Clari (n = 22)	Cipro (n = 20)	Clari (n = 2)	Cipro (n = 4)	Clari (n = 4)	Cipro (n = 3)	Clari (n = 40)	Cipro (n = 44)	Clari (n = 45)	Cipro (n = 41)
Sex (M/F)	6/11	13/6	9/10	11/7	15/6	11/10	12/10	16/4	0/2	4/0	3/1	1/2	21/19	28/16	24/21	28/13
Mean (SD) age (years)	64.1 (13.2)	63.8 (11.2)	62.1 (9.9)	66.3 (9.6)	63.2 (9.5)	59.9 (10.1)	64.8 (11.3)	66.4 (7.9)	75.5 (6.4)	72.0 (5.1)	62.3 (6.4)	61.7 (2.5)	64.2 (11.2)	62.7 (10.7)	63.4 (10.4)	66.0 (8.4)
BCG vaccination	5 (29%)	3 (16%)	5 (26%)	1 (6%)	5 (24%)	2 (10%)	2 (9%)	0 (0%)	1 (50%)	1 (25%)	0 (0%)	0 (0%)	11 (28%)	6 (14%)	7 (16%)	1 (2%)
Cavitation	14 (82%)	12 (63%)	10 (53%)	13 (72%)	11 (52%)	11 (52%)	6 (27%)	7 (35%)	2 (100%)	2 (50%)	2 (50%)	2 (67%)	27 (68%)	25 (57%)	18 (40%)	22 (54%)
⩾3 zones	2 (12%)	6 (32%)	7 (37%)	5 (28%)	3 (14%)	2 (10%)	3 (14%)	1 (5%)	1 (50%)	2 (50%)	0 (0%)	1 (33%)	6 (15%)	10 (23%)	10 (22%)	7 (17%)
Other pulmonary disease on chest radiograph	8 (47%)	10 (53%)	9 (47%)	10 (56%)	9 (43%)	9 (43%)	6 (27%)	7 (35%)	1 (50%)	3 (75%)	4 (100%)	2 (67%)	18 (45%)	22 (50%)	19 (42%)	19 (46%)

Cipro, ciprofloxacin; Clari, clarithromycin; E, ethambutol; R, rifampicin.

Cipro was 15.7% compared with 11.8% for Clari (difference 3.8%; 95% CI −3.2% to 10.8%, p = 0.21).

Good outcome
The differences between REClari and RECipro in terms of those patients classified as "completing treatment as allocated, alive and cured at 5 years" were significant at the 5% level overall (REClari 56 (30.1%) vs RECipro 38 (20.5%), difference 9.7%, 95% CI 0.9% to 18.5%, p = 0.04; table 4). This difference was only observed in those with *M malmoense* (Clari 38.4% vs Cipro 19.8%), with almost identical results for the other two species, but this apparent species × treatment interaction was not statistically significant (p = 0.23, Breslow-Day test). Taking those patients who, regardless of deviations from allocated treatment, were deemed to be "alive and cured at 5 years" (REClari 74 (40%) vs RECipro 61 (33%), table 4), the same pattern of differences was apparent, although not statistically significant (difference 6.8%, 95% CI −3.0% to 16.6%, p = 0.21).

Clinical progress and other indices of outcome
Clinical progress
Overall this was recorded on 856 occasions during the trial. Poor progress was noted on 141 (16.5%) of these, 54 of which were attributed to the mycobacterial disease (6% of all recordings, 38% of poor progress recordings). There was no statistically significant difference between REClari and RECipro in the proportions with poor progress at every time point throughout the follow-up period.

Fourth drug
Of the 32 patients (13 REClari, 19 RECipro) requiring a fourth drug at the end of their first year of treatment, 4 (13%) died from mycobacterial disease compared with 2 of 219 (1%) who had not required a fourth drug ($\chi_c^2 = 11.5$, p = 0.001). No difference was found in all-cause mortality between those requiring the fourth drug and those in whom it was not deemed necessary.

Weight changes
Of those who relapsed (n = 16), 38% had lost 3 kg or more at the time of their relapse compared with 25% of those cured at 5 years (n = 91). Of those cured, 51% had gained 3 kg or more compared with 13% of those who had relapsed ($\chi_{trend}^2 = 5.0$, p = 0.03). A comparison of these groups based on weight changes at the end of their 2 years of treatment showed a similar pattern ($\chi_{trend}^2 = 4.0$, p = 0.046).

DISCUSSION
In the tradition of randomised controlled trials conducted by the British Thoracic Society, this study was set up to compare two promising antibiotic drugs in the context of chemotherapy for the treatment of opportunistic mycobacterial infections and to gather evidence for the benefit of immunotherapy with *M vaccae*. The likely level of recruitment to the trial was unknown, but the subcommittee planning the study took the view that it was preferable to collect data from a randomised prospective comparison than to collect observational data or no data at all. It is debatable whether such a view would be acceptable to a modern ethics committee, but the result was the largest ever randomised trial investigating the treatment of pulmonary disease due to MAC, *M malmoense* or *M xenopi* in the setting of routine chest clinics.

Table 3 Results during and after treatment among those entering the immunotherapy randomisation

| | M avium intracellulare RE | | | | M malmoense RE | | | | M xenopi RE | | | | All 3 species RE | | | | All 3 RE | |
| | M vaccae | | No M vaccae | | M vaccae | | No M vaccae | | M vaccae | | No M vaccae | | M vaccae | | No M vaccae | | M vaccae | No M vaccae |
	Clari	Cipro	Clari	Cipro	Clari	Cipro	Clari	Cipro	Clari	Cipro	Clari	Cipro	Clari	Cipro	Clari	Cipro		
No entered	17	19	19	18	21	21	22	20	2	4	4	3	40	44	45	41	84	86
No deviated*	6 (35%)	7 (37%)	4 (21%)	5 (28%)	5 (24%)	9 (43%)	4 (18%)	12 (60%)	2 (100%)	2 (50%)	3 (75%)	1 (33%)	13 (33%)	18 (41%)	11 (24%)	18 (44%)	31 (37%)	29 (34%)
4th drug required (added)	2 (2)	4 (3)	3 (3)	2 (2)	0	1 (0)	2 (2)	1 (1)	0	1 (1)	0	0	2 (2)	6 (4)	5(5)	3 (3)	8 (6)	8 (8)
Deaths from all causes	7 (41%)	5 (26%)	8 (42%)	6 (33%)	9 (43%)	12 (57%)	8 (36%)	14 (70%)	1 (50%)	2 (50%)	1 (25%)	1 (33%)	17 (43%)	19 (43%)	17 (38%)	21 (51%)	36 (43%)	38 (44%)
Deaths due to mycobacterial disease	1	1	1	0	1	1	1	0	0	1	0	0	2	3	2	0	5	2
Failures of treatment	0	5	1(D)	1	0	0	0	1	0	1	0	0	0	6	1(D)	2	6	3(1D)
Relapses	1	1	3	0	0	0	1	0	0	0	0	0	1	1	4	0	2	4
No completed treatment as allocated and alive and cured at 5 years	7 (41%)	4 (21%)	6 (32%)	6 (33%)	8 (38%)	4 (19%)	10 (45%)	2 (10%)	0 (0%)	0 (0%)	1 (25%)	1 (33%)	15 (38%)	8 (18%)	17 (38%)	9 (22%)	23 (27%)	26 (30%)
No alive and cured at 5 years	8 (47%)	5 (26%)	6 (32%)	7 (39%)	10 (48%)	5 (24%)	13 (59%)	4 (20%)	1 (50%)	1 (25%)	2 (50%)	2 (67%)	19 (48%)	11 (25%)	21 (47%)	13 (32%)	30 (36%)	34 (40%)

Clari, clarithromycin; Cipro, ciprofloxacin; D, death due to mycobacterial disease; E, ethambutol; R, rifampicin.
*Reasons for deviation are detailed in the second section of the Results.

Table 4 Results for all patients during and after treatment

	All Clari (n = 186)				All Cipro (n = 185)				All (n = 371)
	MAC	*M maloense*	*M xenopi*	All 3 species	MAC	*M maloense*	*M xenopi*	All 3 species	Total
No entered	83	86	17	186	87	81	17	185	371
No deviated*	29 (35%)	21 (24%)	10 (59%)	60 (32%)	37 (43%)	35 (43%)	8 (47%)	80 (43%)	140 (38%)
4th drug required (added)	10 (10)	3 (3)	0	13 (13)	15 (13)	3 (2)	1 (1)	19 (16)	32 (29)
Deaths from all causes	40 (48%)	36 (42%)	5 (29%)	81 (44%)	26 (30%)	45 (56%)	8 (47%)	79 (43%)	160 (43%)
Deaths due to mycobacterial disease	2	4	0	6	3	2	1	6	12
Failures of treatment	4 (1D)	1 (1D)	2	7 (2D)	13	4	1	18	25 (2D)
Relapses	7	3 (1D)	2	12 (1D)	7 (2D)	0	0	7 (2D)	19 (3D)
No completed treatment as allocated and alive and cured at 5 years	20 (24%)	33 (38%)	3 (18%)	56 (30%)	20 (23%)	16 (20%)	2 (12%)	38 (21%)	94 (25%)
No alive and cured at 5 years	26 (31%)	42 (49%)	6 (35%)	74 (40%)	30 (34%)	25 (31%)	6 (35%)	61 (33%)	135 (36%)

Clari, clarithromycin; Cipro, ciprofloxacilin; D, death due to mycobacterial disease; MAC, *Mycobacterium avium intracellulare*.
*Reasons for deviation are detailed in the second section of the Results.

Immunotherapy with four doses of *M vaccae* over the first 6 months of chemotherapy did not improve the outcomes of either chemotherapy regimen or overall outcome. Initially a promising modality of treatment with which to supplement chemotherapy for mycobacterial disease,[12–15] immunotherapy with *M vaccae* has not fulfilled expectations when used in the treatment of tuberculosis.[16–19] The same disappointing result has now been demonstrated in a large prospective trial of treatments for pulmonary disease caused by MAC, *M malmoense* and *M xenopi*. It is possible that shorter intervals between doses of *M vaccae* and/or administration for longer might have produced different results but, as things stand currently, immunotherapy with *M vaccae* cannot be recommended as part of the treatment of patients with lung disease caused by MAC, *M malmoense* and *M xenopi*.

Over the three species combined, REClari and RECipro did not differ meaningfully in terms of deaths due to mycobacteria, failures of treatment + relapses and deaths due to all causes. More patients on REClari than on RECipro completed treatment as allocated and were alive and cured at the end of 5 years (30.1% vs 20.5%, p = 0.04); this effect stemmed from the results in patients with *M malmoense* and was not evident for those with MAC or *M xenopi*. In the previous BTS study of the treatment of MAC, *M malmoense* and *M xenopi*, it was shown that there was no correlation between clinical outcome and the results of susceptibility tests to the antimycobacterial drugs R, H and E when tested singly in vitro.[1] In laboratory studies the combination of R and E has been found to act synergistically in vitro against opportunist mycobacteria,[20–22] and in the first BTS study this combination ($\pm$H) resulted in outcomes better than those achieved by earlier five- or six-drug regimens.[1 23–28] It was hoped that triple drug regimens containing Clari and Cipro in combination with RE might prove more effective than RE alone or REH, but this does not appear to be the case (table 5).

With the regimens used in this trial, the frequency of unwanted effects leading to a change of treatment were twice that encountered with RE and REH.[1] Although the REClari and RECipro groups were little different from each other in this respect, in the REClari group there was a trend for more patients to experience unacceptable unwanted effects attributed to E than was the case for the RECipro group, especially visual problems. The protocol did not require ophthalmological opinion or measurement of E levels for patients with visual problems, but enquiry after the end of the trial indicated that not all of these visual problems were truly related to E.

Adjustment of the figures to take account of this information resulted in loss of statistical significance of the difference between REClari and RECipro. Physicians using E in the treatment of mycobacterial disease are very aware of its potential effects on the eyes and perhaps tend to err on the side of caution, stopping the drug unnecessarily in some instances.

Mortality rates at 5 years were over 40%, as they had been in the earlier trial, the majority dying from causes other than the mycobacterial disease. Deaths attributed to opportunist mycobacterial disease were uncommon but were more frequent in those who still had sputum which was culture positive for mycobacteria at 12 months. Until new drugs are developed which can supplement those currently available for treating patients with these diseases, physicians are left with the common sense measure of improving general health and optimising treatment of concomitant diseases as the only other options with potential for further reducing mortality and morbidity, focusing particularly on those not doing well at 12 months.

The BTS guidelines for the treatment of these conditions recommended RE as a regimen which improved outcome compared with no treatment or treatment which included four, five or six drugs chosen on the basis of in vitro susceptibility tests.[29] Table 5 shows the outcomes for each species with each of four regimens (RE and REH from the previous study[1] and REClari and RECipro from the current study). Comparisons of these outcomes can only be cautiously interpreted as they are derived from different trials and, in deciding on which regimen to choose initially, account should be taken of the increased incidence of unwanted effects with the Clari or Cipro regimens. For MAC, REClari was associated with an all-cause death rate higher than with any other regimen, whereas more patients had a "good outcome" with REH. However, the death rate due to mycobacterial disease was higher with REH than with RE. Perhaps the "best buy" initial regimen could be RE, adding H or Cipro if the patient is not doing well at 12 months. For *M malmoense*, the "all-cause death rate" with RECipro was higher than with the other regimens. There appears to be little to choose between RE, REH and REClari in terms of efficacy, but unwanted effects were more frequent with REClari. For *M xenopi*, REClari appears best in terms of efficacy but would be likely to carry more risk of unwanted effects than RE.

This largest ever randomised trial, performed in the setting of routine chest clinics, has provided further evidence to guide

Table 5 Comparative outcomes of four regimens in the treatment of lung diseases caused by MAC, *M malmoense* and *M xenopi*

	MAC				M malmoense				M xenopi				Total
	RE	REH	REClari	RECipro	RE	REH	REClari	RECipro	RE	REH	REClari	RECipro	
No of patients	37	38	83	87	52	54	86	81	22	20	17	17	594
Deviated from protocol	16%	21%	35%	43%	29%	22%	24%	43%	14%	25%	59%	47%	32%
Deaths (all causes)	32%	39%	48%	30%	33%	35%	42%	56%	55%	85%	29%	47%	42%
Deaths (due to mycobacteria)	0%	8%	2%	3%	2%	6%	5%	2%	0%	15%	0%	6%	4%
Failures of treatment and relapses	41%	16%	13%	23%	12%	9%	5%	5%	18%	5%	24%	6%	14%
Completed treatment as allocated, alive and cured at 5 years	27%	34%	24%	23%	38%	44%	38%	20%	23%	10%	18%	12%	28%

Clari, clarithromycin; Cipro, ciprofloxacin; H, isoniazid; E, ethambutol; MAC, *Mycobacterium avium intracellulare*; R, rifampicin.
Percentages do not always add up to 100% because some patients who died had earlier been failures of treatment or relapses.

clinicians managing these conditions. However, the outlook for patients with pulmonary disease due to MAC, *M malmoense* or *M xenopi* treated with currently available drugs continues to be poor. As these diseases appear to be markers of poor health, studies of various methods of optimising general health and of managing co-morbidity in this population are needed, just as much as research into better antimycobacterial drugs with which to devise new regimens for testing in clinical trials.

Competing interests: None.

Contributors: The first draft of the protocol was written by IAC and modified after discussion by the subcommittee. Data entry was overseen by IAC. RJP supervised data checking and performed the statistical analyses. The first draft of the report was produced by IAC, who made amendments in the light of discussion and comment by the subcommittee. The penultimate draft was scrutinised by the Research Committee and the final version then prepared by IAC.

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CORRECTIONS

L Paleari, A Cesario, P Granone, *et al*. Early detection of cancer: lessons from lung cancer CT screening. *Thorax* 2008;**63**:566. The correct affiliation for the fifth author, Patrizia Russo, is Lung Cancer Unit, National Cancer Institute, Genoa, Italy.

P A Jenkins, I A Campbell, J Banks, *et al*. Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of *Mycobacterium vaccae* immunotherapy. *Thorax* 2008;63:627–34. There is an error in the abstract of this article. It should read as follows. A trial was undertaken to compare clarithromycin (Clari) and ciprofloxacin (Cipro) as third drugs added to 2 years of treatment with R and E for pulmonary disease caused by *M avium-intracellulare* (MAC), *M malmoense* and *M xenopi* (REClari and RECiprol).

Pulmonary puzzle

ANSWER

From the question on page 802.

Two small opacities are seen in the nasopharynx.

Using fluoroscopy, an ENT surgeon was able to identify the presence of a nasal clip (fig 1) which was removed without difficulty, hence allowing NIV to continue. The patient had been using the device at night to keep his nasal flares patent to help alleviate snoring; he had nasally inhaled the clip with the added positive pressure of his ventilator. The presence of a foreign body either in the upper or lower respiratory tract must always be eliminated when signs of respiratory distress are observed. Assessment is particularly difficult in patients with limited communication such as those with bulbar disease of whatever cause.

Snoring is a extremely common condition that can cause significant difficulties in relationships and home life. Despite very limited evidence, there are numerous commercially available mechanical aids that attempt to keep the nasal air passages clear. When initiating non-invasive ventilation or continuous positive airways pressures therapy, one should check with the patient that these aids are not being used at night due to the risk of aspiration with added positive pressure.
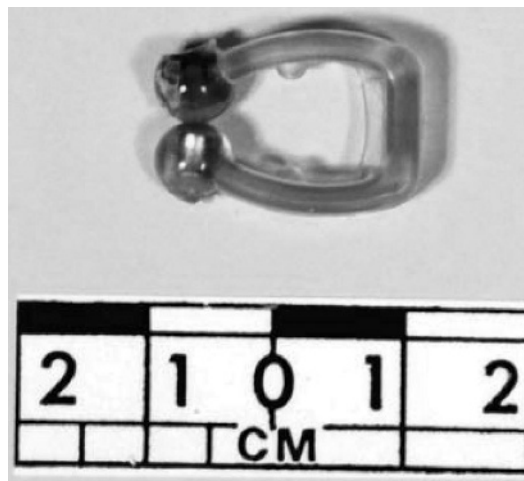

Figure 1 Nasal clip device after its removal.