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A bacteriological survey of tuberculosis due to the human tubercle bacillus (*Mycobacterium tuberculosis*) in South-East England: 1984–91

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SUMMARY

The occurrence and nature of bacteriologically confirmed tuberculosis due to *Mycobacterium tuberculosis* in South-East England in the period 1984–91 is reported and compared with the results of a study for 1977–83. Registered new cases reached a low of 1028 in 1988 but increased to 1252 in 1991. This appeared to be due to a halt in the previous decline in new cases of European patients, a small increase in the number of Indian subcontinent (ISC) patients and an increase in patients from Africa. A total of 122 patients, mostly of European ethnic origin, were known to be HIV positive. As in the 1977–83 study, disease in the ISC group affected younger patients than in the European group, tubercle bacilli were more frequently isolated from a non-pulmonary site in the ISC group (45%) than in the European group (19%) and there was a higher incidence of the South Indian variant of *M. tuberculosis* in the former group (17%) than in the latter (9%). The overall incidence of drug resistance has not altered significantly since the 1977–83 study but 46 strains resistant to 3 or more drugs were isolated from 4099 ISC patients, compared with 3 of 4594 strains from European patients. Six of the 122 isolates from HIV positive patients were drug-resistant but none was multi-drug resistant.

The slight rise in registered bacteriologically proven cases of tuberculosis, the presence of multi-drug resistant strains, the occurrence of HIV-related tuberculosis and reports of the emergence of multi-drug-resistant HIV-related tuberculosis in other countries strongly indicate the need for continued careful surveillance.

INTRODUCTION

The World Health Organisation and the International Union Against Tuberculosis and Lung Disease have stressed the importance of surveillance of tuberculosis in the industrialized nations during the final stages of elimination of this disease [1]. In the UK, surveillance is officially done through the statutory

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notification system which can be used as the basis for surveys of the nature and incidence of tuberculosis [2]. In practice, however, not all cases are reported. Bacteriological examination, although not positive in all cases of tuberculosis, supplies useful information not provided by the notification system; for example, the types of bacillus and changing trends in drug resistance. In addition, a definitive diagnosis can only be achieved by bacteriology. In view of the concern over the high incidence of tuberculosis among immigrants of Indian subcontinent (ISC) ethnic origin in the early to mid 1970s, we undertook a survey of all strains of *Mycobacterium tuberculosis* sent to the PHLS South East Regional Tuberculosis Centre between 1977 and 1983 [3]. That survey revealed that about one third of all isolates were from ISC patients and that a relatively high proportion of isolates from that group of patients was from non-pulmonary lesions. The South Indian type of *M. tuberculosis*, characterized by susceptibility to thiophen-2-carboxylic acid hydrazide (TCH) was more prevalent in the ISC group than in the European group but there was no relation between the type of bacillus and the site of disease.

As the previous decline in the incidence of tuberculosis has halted in some industrialized countries including the UK [4], and in view of the well-documented effect of the HIV pandemic on the incidence of tuberculosis [5] we have completed a further survey, based on identical methods to those used in the previous study, for the period 1984–91.

MATERIALS AND METHODS

The PHLS South East Regional Tuberculosis Centre receives mycobacteria isolated by about 90 client laboratories in London and South-East England. All referred strains are first divided into members of the tuberculosis complex (*M. tuberculosis*, *M. bovis*, *M. africanum* and BCG) and the environmental ('atypical') mycobacteria. Members of the former complex are slow growing and non-pigmented and they fail to grow at 25 °C and on media containing 500 mg/l of *p*-nitrobenzoic acid [6].

Strains belonging to the tuberculosis complex are then subdivided for epidemiological purposes by four tests; namely, oxygen preference, nitratase activity, susceptibility to thiophen-2-carboxylic acid hydrazide (TCH) and susceptibility to pyrazinamide, as described previously [7] and summarized in Table 1. They are also tested for susceptibility to anti-tuberculosis drugs.

In this study, an analysis of isolates of the classical (TCH resistant) and South Indian (TCH susceptible) strains of *M. tuberculosis* from new cases of tuberculosis is presented. Isolates of the other two species in the tuberculosis complex (*M. bovis* and *M. africanum*) were excluded.

Information supplied by the referring laboratories included the name, age and sex of the patient and the site(s) of isolation of the organism. Most of the client laboratories inform the reference centre if the patient is known to be HIV positive. Patients were divided into those of European, African, Indian subcontinent (ISC) and other ethnic origins on the basis of their names.

The significances of differences in the various groups was determined by the use of the χ^2 test with Yates' correction and Fisher's exact test, as indicated in the text.

Table 1. *Subdivision of the tuberculosis complex*

Type of tubercle bacillus	Oxygen preference*	Nitratase†	Susceptibility to TCH‡	Susceptibility to pyrazinamide
Classical human (*M. tuberculosis*)	Aero	Pos	Res	Sens
Asian (*M. tuberculosis*)	Aero	Pos	Sens	Sens
African I (*M. africanum*)	Micro	Neg	Sens	Sens
African II (*M. africanum*)	Micro	Neg	Sens	Sens
Bovine (*M. bovis*)	Micro	Neg	Sens	Res
BCG	Aero	Var	Sens	Res

* Aero, aerophilic; Micro, microaerophilic.
† Pos, positive; Neg, negative; Var, variable reactivity.
‡ Res, resistant; Sens, sensitive.

Table 2. *Annual incidence of strains according to ethnic origin and sex of the patient, site of isolation (pulmonary or non-pulmonary) and susceptibility of the organism to TCH*

	Year							
Group	1984	1985	1986	1987	1988	1989	1990	1991
Total	1183	1236	1206	1148	1028	1088	1178	1252
Ethnic origin								
European	626	671	613	607	482	524	555	517
ISC	512	504	533	471	486	494	494	605
African	12	22	17	27	28	38	83	88
Far East	28	31	38	34	28	26	46	40
Other	5	8	5	9	4	6	0	2
Sex*								
Male	688	720	704	687	608	654	697	738
Female	461	497	481	438	390	398	456	473
Site								
Pulmonary	819	853	818	760	677	730	807	795
Non-pulmonary	364	383	388	388	351	358	371	457
TCH susceptibility								
Resistant	986	1008	1021	972	865	926	930	1015
Susceptible	192	226	184	173	162	160	248	233
Both†	5	2	1	3	1	2	0	4

* These numbers are less than the total as information was not available for every patient.
† Two or more isolates of differing susceptibilities.

RESULTS

The annual numbers of new cases of tuberculosis according to ethnic origin registered at Dulwich are shown in Table 2. These numbers reached a low of 1028 cases in 1988 but increased over the subsequent 3 years to 1252 cases in 1991. The annual numbers of new cases of tuberculosis in those of European and ISC ethnic origin over this and, for comparison, the period of the previous survey, and of those of African ethnic origin for this survey, are shown in Fig. 1. The annual number of ISC patients has been fairly constant since 1981 while the number of

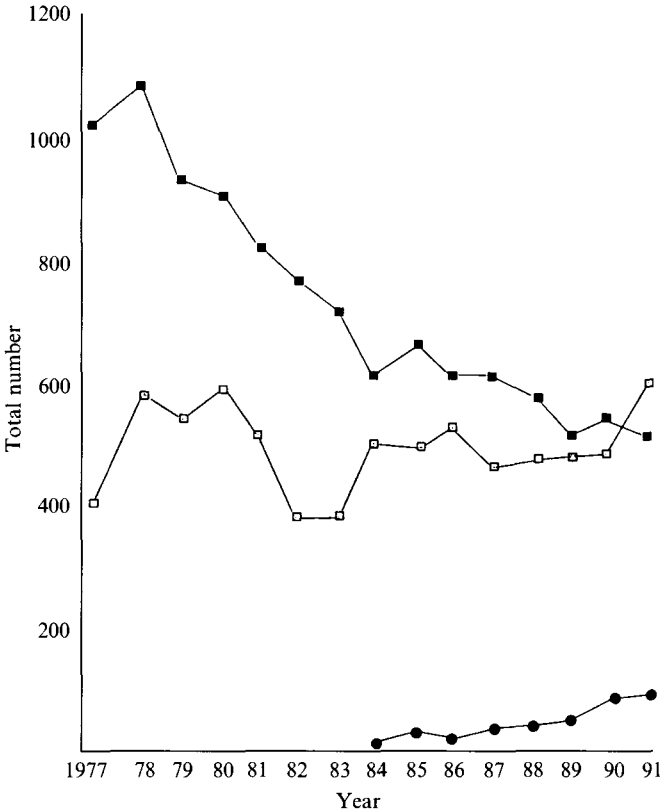

Fig. 1. Annual numbers of patients of European and Indian subcontinent (ISC) ethnic origin 1977–91 and those of African ethnic origin 1984–91. ■——■, European; □——□, ISC; ●——●, African.

European patients has been declining. In 1991, for the first time, there were slightly more ISC than European ethnic patients. In addition, there has been an increase in the number of African patients, particularly in the last 2 years.

Fig. 2 shows the age distribution of patients in the ISC and European groups. The ISC group shows a peak in the 20–30 age group while the European group shows two peaks, one in the 20–30 age group and a more diffuse peak in the older age group.

Fig. 3 shows annual numbers of new cases of male and female patients of European ethnic origin after division into those aged up to 45 years and over 45. There was a decline in the annual numbers of new cases in the older age groups, but not in the younger age group, for both sexes. The corresponding distributions for patients of other ethnic origins are not shown as these groups are affected by changing immigration patterns.

The distribution of strains according to the sex of the patient and the site of the disease are shown in Table 3. Males predominated in all ethnic groups and non-pulmonary lesions were more frequent in non-European groups, notably the ISC group. Strains susceptible to thiophen-2-carboxylic acid hydrazide (TCH) were present in all four groups, but were least frequent in the European group. In the 1977–83 survey, the percentages of TCH susceptible strains in the European and

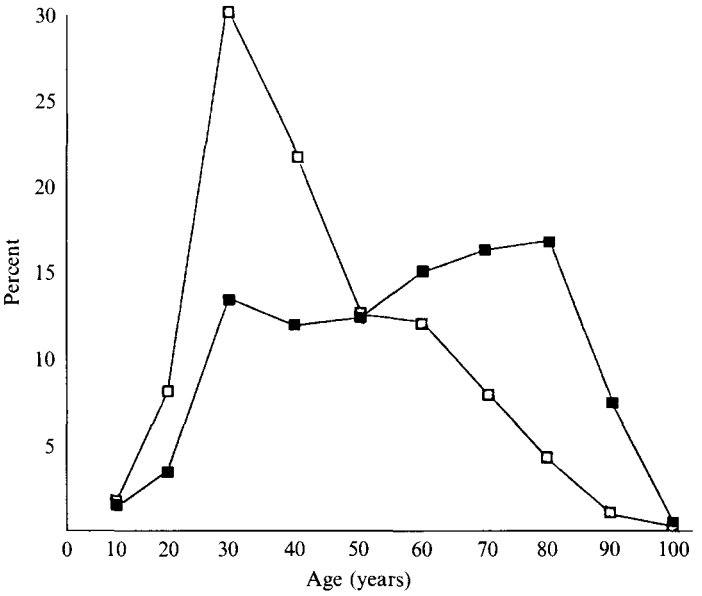

Fig. 2. Age distribution of patients of European and Indian subcontinent (ISC) ethnic origin 1984–91; ■——■, European; □——□, ISC.

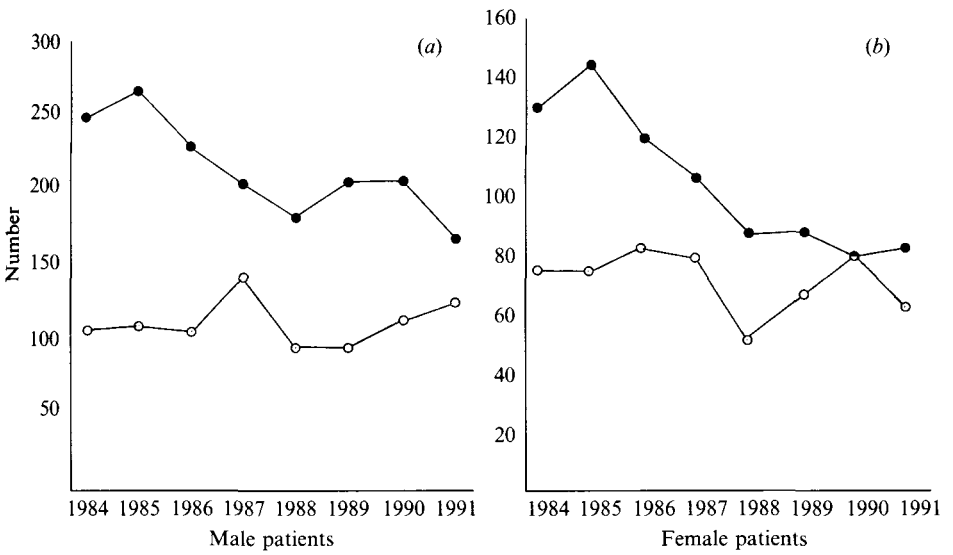

Fig. 3. Annual incidence of tuberculosis in (*a*) male and (*b*) female patients of European ethnic origin aged 45 or less (○——○) and over 45 (●——●).

ISC groups were 9 and 17 respectively, thus the proportion has risen slightly but significantly in both groups (European, χ^2 12·1, $P < 0{\cdot}001$; ISC, χ^2 21·9, $P < 0{\cdot}001$).

The sites of the non-pulmonary lesions in the two surveys are shown in Table 4. The previously observed high proportion of non-pulmonary disease in the ISC group has decreased from 49·5% of all isolates to 45% (χ^2 22·4, $P < 0{\cdot}001$) – this decrease being most evident in respect to bone and joint disease. In the European

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Table 3. *Sex of patient, site of lesion and susceptibility of the organism to thiophen-2-carboxylic acid hydrazide (TCH) according to ethnic origin of the patient (percentages in parentheses) for the period 1984–91*

	European	ISC	African	Far East
Male	3039 (66)	2113 (54)	168 (55)	141 (60)
Female	1538 (34)	1813 (46)	137 (45)	95 (40)
Total	4577	3926	305	236
Pulmonary	3685 (81)	2182 (55)	203 (64)	175 (65)
Non-pulmonary	861 (19)	1794 (45)	112 (36)	95 (35)
Total	4546	3976	315	270
TCH positive	4085 (89)	3198 (78)	238 (76)	166 (61)
TCH negative	503 (11)	891 (22)	76 (24)	104 (39)
Both	6 (< 1)	10 (< 1)	1 (< 1)	1 (< 1)
Total	4594	4099	315	271

Table 4. *Percentage distribution of non-pulmonary tuberculosis in the European and Indian Sub-Continent (ISC) ethnic groups for the periods 1977–83 and 1984–91*

	European		ISC	
	1977–83	1984–91	1977–83	1984–91
Lymph node	30·3	36·6	55·6	59·6
Bone and joint	19·5	19·7	24·7	19·2
Genitourinary	37·6	27·2	6·8	8·4
Abdomen	5·1	7·8	7·8	8·3
CNS	6·7	4·4	4·3	3·7
Disseminated	0·8	4·2	0·7	0·6
Actual numbers	1470	861	1914	1794
% of total	21·3	18·9	49·5	45·1

Table 5. *Number of cases of HIV-related tuberculosis (number of females in parentheses) notified to the South-East Regional Centre for Tuberculosis Bacteriology*

Year	European	Asian	African	Far East	Total
1984	2				2
1985	4				4
1986	7				7
1987	16*	1			17
1988	10 (1)	2 (1)	4 (2)	1	17 (4)
1989	19	2	4 (1)		25 (1)
1990	17 (2)	2	4 (1)		23 (3)
1991	19 (3)	2	5	1	27 (3)
Total	94 (6)	9 (1)	17 (4)	2	122 (11)

* 1 sex unknown.

group the relative number of non-pulmonary cases had also declined (from 21·3% to 18·9%, χ^2 9·89, $P < 0{\cdot}01$): the proportion of cases of genito-urinary tuberculosis was lower but that of lymph node disease was higher.

The site distribution in the present survey differed according to the sex of the patients, particularly European patients, in whom the relative proportion of

Table 6. *Drug resistance in South-East England: 1984–91*

Ethnic group	1 drug*					2 drugs				3 drugs	4 drugs	5 drugs	6 drugs	% of total
	H	S	Z	R	E	H+S	H+R	S+R	Other	(no. resistant to rifampicin in parentheses)				(% 1977–83)
European	60	30	15	3	1	16	4	—	1	1 (1)	1 (1)	1 (1)		2·9 (2·6)
ISC†	119	72	12	5	—	83	4	1	6	28 (11)	14 (13)	3 (3)	1 (1)	8·5 (8·3)
African	10	8	—	1	—	13	2	—	—	1 (1)	—	—	—	11·4
Far East	6	11	1	—	—	9	—	—	—	—	4 (4)	—	—	11·4
Other	—	2	1	—	—	—	2	—	—	—	1 (1)	1 (1)	—	17·9

* H, isoniazid; S, streptomycin; Z, pyrazinamide; R, rifampicin; E, ethambutol.
† ISC, Indian subcontinent.

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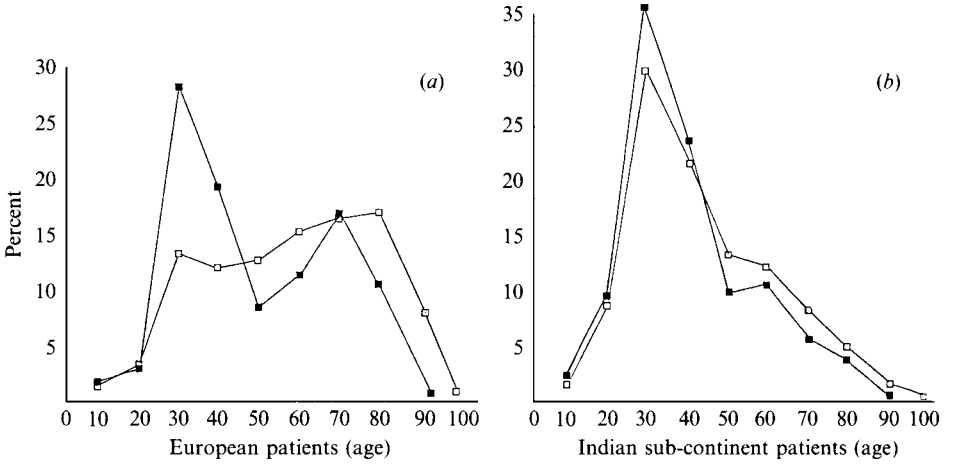

Fig. 4. Age distribution of patients of (*a*) European and (*b*) Indian subcontinent (ISC) ethnic origin with drug susceptible and resistant strains 1984–91. □——□. Susceptible; ■– – –■. resistant.

lymph node disease was higher in females than in males (43 *v.* 27%; χ^2 26·2. $P < 0{\cdot}001$) but that of genito-urinary disease was lower in females (15 *v.* 35%. χ^2 47·7, $P < 0{\cdot}001$). The corresponding trends were less evident in the ISC group: 59 *v.* 53% and 7 *v.* 9% respectively.

The numbers of cases of known HIV-related tuberculosis are shown in Table 5. The cases appear to have reached a plateau in 1989. Most patients were male and European. The mean age was 34 years, with a range from 21 to 65 years of age: 63 isolates were from the lung, 21 from lymph nodes, 9 from other discrete non-pulmonary sites and 29 were cases of disseminated disease. On the basis of information on the site of isolation, these figures may underestimate the frequency of disseminated disease.

The numbers of drug resistant strains are shown in Table 6. The numbers for the European and ISC groups show a slight increase from the 1977–83 figures (from 2·6 to 2·9% and 8·3 to 8·5% respectively) but these increases are not statistically significant. Amongst Europeans, most resistance was to isoniazid, streptomycin or both. There were a very few rifampicin-resistant strains and multi-drug resistant strains, defined as strains resistant to more than two drugs. More multi-drug resistance was seen in the ISC group. Twenty-two Nepalese patients, referred from the Royal Army Medical Corps, were excluded from this analysis as they had a high incidence of drug resistance, including multi-drug resistance, but represented a special group of temporary residents. The incidence of drug resistance was higher among strains from pulmonary lesions than from non-pulmonary lesions: 3·2 *v.* 1·7% in European patients (χ^2 5·24, $P < 0{\cdot}05$) and 10·4 *v.* 6·8% in ISC patients (χ^2 15·6, $P < 0{\cdot}001$). The incidence was also higher among TCH resistant strains than TCH sensitive strains in the ISC group (9·8 *v.* 3·8%; χ^2 312·4, $P < 0{\cdot}001$).

Six drug-resistant strains were isolated from amongst the 122 HIV-positive patients. Three of the 17 strains (21%) from Africans were resistant (1 to isoniazid plus streptomycin and 2 to isoniazid alone) and 3 of the 92 strains (11%) from Europeans were resistant (2 to isoniazid alone and 1 to rifampicin alone). The

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incidence of resistance in both ethnic groups was higher than that in patients not known to be HIV positive but the difference was not statistically significant (Fisher's exact test).

The incidence of drug resistance according to age of the patient is shown in Fig. 4. This incidence was not particularly age-related in the ISC group but in the European group there was a distinct tendency for resistant strains to occur in the younger age group.

DISCUSSION

Bacteriologically confirmed tuberculosis in South-East England has shown a slight increase since 1988. This appears to be due to a levelling off of the previous decline in the annual numbers of new cases of European patients, a small increase in the number of Indian subcontinent patients and an increase in patients from Africa. From data supplied to us, HIV-related tuberculosis is not a serious problem at present but the reported cases may be an underestimate of the total and therefore close surveillance will be required in the future. Other possible factors affecting the trends include lack of diagnostic awareness, permitting dissemination of disease, and increasing poverty and overcrowding with poor provision of health care services to homeless and other disadvantaged persons.

The trends with respect to age and site distribution in the European and Indian subcontinent ethnic groups in the period covered by this study were broadly similar to those in the preceding period, 1977–83. Drug resistance was increased slightly, with several multi-drug resistant strains in the Indian subcontinent ethnic group.

Susceptibility to thiophen-2-carboxylic acid hydrazide (TCH) has been used to subdivide strains of *M. tuberculosis* into the Classical and South Indian types. The proportion of the latter type in the Indian subcontinent ethnic group is about double that in the European ethnic group and relatively large numbers were found in the African and Far East ethnic groups. In a few cases, susceptible and resistant bacilli were isolated from the same patient but it is not known whether this is due to multiple infections or to selection of mutants. As in the 1977–83 study, drug resistance was more frequent among isolates from the lung than those from non-pulmonary sites and also more frequent among TCH resistant than sensitive strains. Despite a chemical similarity, resistance to TCH is independent of that of isoniazid [8].

As in the previous survey, patients of ISC ethnic origin are of a younger age group than those of European ethnic origin. This could reflect differences in the age distribution of the respective total population, a higher annual risk of infection in the ISC group and the presence of more infected persons immigrating from countries with high incidences of tuberculosis. The reasons for the different distributions of disease according to site of lesions and sex of the patients, and the factors controlling the distribution of the TCH susceptible and resistant strains, remain unknown.

The incidence of drug resistance has not altered significantly since the 1977–83 study. The unexplained higher incidence of drug resistant strains among younger patients of European ethnic origin is, nevertheless, cause for concern and the responsible factors require elucidation. The incidence of drug resistance among

strains from the known HIV positive patients (6 of 122) was higher than in the other patients but, in view of the small numbers, this could well be due to chance. Multi-drug resistance is a serious problem among HIV-positive tuberculosis patients in New York [9] but is not one that has yet been encountered in this region.

Other members of the tuberculosis group have also been isolated from patients in South East England. About 1·2% of all isolates were identified as *M. bovis* [10] and 1·25% as *M. africanum* [11] in the same study period.

The accuracy of information on the nature and incidence of tuberculosis obtained from bacteriological surveys is affected by many factors. Bacteriological confirmation is not obtained in all cases, particularly in childhood and non-pulmonary disease and the isolation rate from specimens varies according to the number and quality of specimens and local laboratory practices. Surveys based on notification, although providing useful information [2] are likewise prone to many inaccuracies. Ideally, there should be an integrated system for the registration of both notified and bacteriologically confirmed patients by name and reference number so that surveillance could be based on a composite of the two data-collecting methods.

In conclusion, South East England has experienced a slight increase in the annual numbers of new cases of bacteriologically confirmed tuberculosis over the last 3 years. Although a few multi-drug resistant strains have been detected, the region is not faced with the serious problems of emergent drug resistance that have been encountered elsewhere. Nevertheless, there is no place for complacency as the future trends of the disease are unpredictable. There is a need for 'less speculation and better surveillance' [12] and this must include bacteriological surveys.

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