Thrombose de Bretagne Occidentale. *Thromb Haemost* 2000;83:657-60.
10 Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004;292:1573-80.
11 Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;136:680-90.
12 Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. *JAMA* 2002;288:872-81.
13 Gomes MP, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. *Arch Intern Med* 2004;164:1965-76.
14 Wu O, Robertson L, Langhorne P, Twaddle S, Lowe GD, Clark P, et al. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. *Thromb Haemost* 2005;94:17-25.
15 Lowe GD, Upton MN, Rumley A, McConnachie A, O'Reilly DS, Watt GC. Different effects of oral and transdermal hormone replacement therapies on factor IX, APC resistance, t-PA, PAI and C-reactive protein—a cross-sectional population survey. *Thromb Haemost* 2001;86:550-6.
16 Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arterioscler Thromb Vasc Biol* 1997;17:3071-8.
17 Oger E, Alhenc-Gelas M, Lacut K, Blouch MT, Roudaut N, Kerlan V, et al. Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among postmenopausal women: a randomized trial. *Arterioscler Thromb Vasc Biol* 2003;23:1671-6.
18 Conard J, Samama M, Basdevant A, Guy-Grand B, de Lignieres B. Differential AT III-response to oral and parenteral administration of 17 beta-estradiol. *Thromb Haemost* 1983;49:252.
19 Rosing J, Middeldorp S, Curvers J, Christella M, Thomassen LG, Nicolaes GA, et al. Low-dose oral contraceptives and acquired resistance to activated protein C: a randomised cross-over study. *Lancet* 1999;354:2036-40.
20 Hoibraaten E, Mowinckel MC, de Ronde H, Bertina RM, Sandset PM. Hormone replacement therapy and acquired resistance to activated protein C: results of a randomized, double-blind, placebo-controlled trial. *Br J Haematol* 2001;115:415-20.
21 Post MS, Christella M, Thomassen LG, van der Mooren MJ, van Baal WM, Rosing J, et al. Effect of oral and transdermal estrogen replacement therapy on hemostatic variables associated with venous thrombosis: a randomized, placebo-controlled study in postmenopausal women. *Arterioscler Thromb Vasc Biol* 2003;23:1116-21.
22 Beral V, Banks E, Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. *Lancet* 2002;360:942-4.
23 Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of the North American Menopause Society. *Menopause* 2007;14:168-82.

Accepted: 26 March 2008

Increasing antituberculosis drug resistance in the United Kingdom: analysis of national surveillance data

Michelle E Kruijshaar,[1] John M Watson,[1] Francis Drobniewski,[2] Charlotte Anderson,[1] Timothy J Brown,[2] John G Magee,[3] E Grace Smith,[4] Alistair Story,[1] Ibrahim Abubakar[1,5]

EDITORIAL by Lewis and Chihota

[1]Respiratory Diseases Department, Centre for Infections, Health Protection Agency, London NW9 5EQ
[2]Mycobacterium Reference Unit, Barts and the London, Queen Mary's School of Medicine and Dentistry, London E1 2AT
[3]Regional Centre for Mycobacteriology, Health Protection Agency North East, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE
[4]Regional Centre for Mycobacteriology, Health Protection Agency, Heart of England NHS Foundation Trust, Birmingham B9 5SS
[5]School of Medicine, Health Policy and Practice, University of East Anglia, Norwich NR4 7TJ
Correspondence to: M E Kruijshaar michelle.kruijshaar@hpa.org.uk

BMJ 2008;336:1231-4
doi:10.1136/bmj.39546.573067.25

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2008, doi: 10.1136/bmj.39546.573067.25

ABSTRACT

Objective To identify recent trends in, and factors associated with, resistance to antituberculosis drugs in England, Wales, and Northern Ireland.

Design Cohort of tuberculosis cases reported to the enhanced tuberculosis surveillance system matched to data on drug susceptibility and national strain typing data.

Setting England, Wales, and Northern Ireland 1998-2005.

Main outcome measures Unadjusted and adjusted odds ratios for drug resistance and associated factors. Proportion of multidrug resistant tuberculosis cases clustered.

Results 28 620 culture confirmed cases were available for analysis. The proportion of cases resistant to isoniazid increased from 5% to 7%. Rifampicin resistance increased from 1.0% to 1.2% and multidrug resistance from 0.8% to 0.9%. Ethambutol and pyrazinamide resistance remained stable at around 0.4% and 0.6%, respectively. Regression analyses showed a significant increase in isoniazid resistance outside London (odds ratio 1.04, 95% confidence interval 1.01 to 1.07, a year, associated with changes in age (0.98, 0.98 to 0.99, a year), place of birth (1.49, 1.16 to 1.92), and ethnicity ($P<0.05$). In London, the rise (1.05, 1.02 to 1.08, a year) was related mainly to an ongoing outbreak. Increases in rifampicin resistance (1.06, 1.01 to 1.11, a year) and multidrug resistance (1.06, 1.00 to 1.12, a year) were small. A fifth of patients with multidrug resistant tuberculosis in 2004-5 had indistinguishable strain types, and one case was identified as extensively drug resistant.

Conclusions The rise in isoniazid resistance reflects increasing numbers of patients from sub-Saharan Africa and the Indian subcontinent, who might have acquired resistance abroad, and inadequate control of transmission in London. The observed increases highlight the need for early case detection, rapid testing of susceptibility to drugs, and improved treatment completion.

INTRODUCTION

Resistance to antituberculosis drugs is increasing globally, and transmission of drug resistant tuberculosis has been shown among marginalised groups in urban areas, such as London.[1 2] Data on drug susceptibility have been routinely collected in the UK since 1993. Drug resistance, including multidrug resistance, remained stable from 1993 to 1999.[3 4] We examined recent trends in resistance to antituberculosis drugs among cases reported in England, Wales, and Northern Ireland from 1998 to 2005 and investigated factors associated with resistance.

METHODS

Data on drug susceptibility for initial isolates were available from the UK Mycobacterial Surveillance Network (MycobNet), which collates information from all UK mycobacterial reference laboratories on first

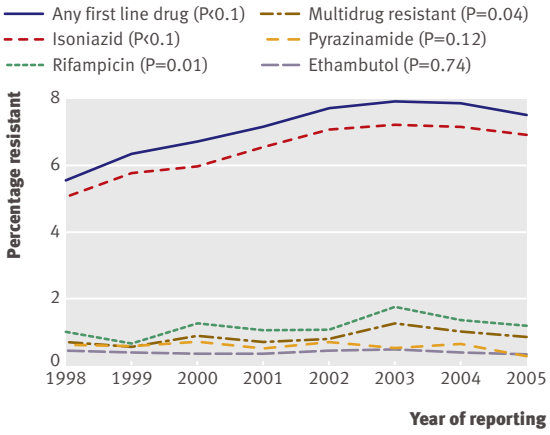

Fig 1 | Proportion of tuberculosis cases confirmed by culture (with test results for both isoniazid and rifampicin) resistant to first line drugs, multidrug resistant, and resistant to any first line drug by year, and significance of trend over time

isolates identified as *Mycobacterium tuberculosis* complex.[3 5] To improve the demographic and clinical information available, we matched MycobNet records to the national enhanced tuberculosis surveillance database,which provides information on cases reported in England and Wales since 1998, and Northern Ireland since 2000.[6]

Tuberculosis cases were either confirmed by culture to be caused by *M tuberculosis* complex or met predefined clinical criteria (see bmj.com).[5] In the UK first line antituberculosis drugs are isoniazid, rifampicin, pyrazinamide, and ethambutol (or more rarely streptomycin). Multidrug resistant tuberculosis is defined as resistance to at least isoniazid and rifampicin and extensively drug resistant tuberculosis as resistance to at least rifampicin, isoniazid, a fluoroquinolone, and one of three injectable second line drugs (amikacin, kanamycin, capreomycin).

We inspected trends in resistance to first line drugs from 1998 to 2005 and tested significance of odds ratios for a linear trend using univariable and multivariable logistic regression modelling. Multivariable models adjusted for age, sex, place of birth (born in the UK or elsewhere), ethnic group, region (London versus outside London), previous diagnosis and factors previously reported to be associated with resistance and included site of disease.[7-9] As we were aware of an outbreak of isoniazid monoresistance in London, with limited evidence of transmission outside London, we stratified analyses for isoniazid resistance by region.[1] Interactions between previous diagnosis, region, place of birth, and ethnic group were investigated and multiple interactions of $P<0.01$ supported stratification of the analyses for London by region.

To identify trends in second line drug resistance and cases of extensively drug resistant tuberculosis, we undertook a review of second line drugs for cases of multidrug resistant tuberculosis for 2002-5. Strain typing information was collated for multidrug resistant cases reported in 2004-5, and analysed to assess recent transmission and the proportion clustered (n−1 method).[10] See bmj.com for further details.

RESULTS

From 1998 to 2005, 34 555 initial isolates were identified as *M tuberculosis* complex and 53 602 cases of tuberculosis were reported to the national surveillance system. Matching of the two databases resulted in 28 620 culture confirmed cases (82.8% of initial isolates; 53.4% of case reports). We included 28 485 cases (99.5% of culture confirmed cases) with susceptibility results for isoniazid and rifampicin in our analyses.

The median age of culture confirmed patients was 35 (interquartile range 26-54); 57% were male (16 164), 69% (17 522) were born outside the UK, 24% of whom entered less than two years before diagnosis; 8% (1889) had had a previous diagnosis of tuberculosis; and 42% (11 851) of cases were reported from London. Similar proportions were seen among cases not confirmed by culture. See bmj.com for full details. Patients with culture confirmed tuberculosis more often had pulmonary disease (67% *v* 50% of all other cases) and more often had positive results on sputum smear tests (61% *v* 26%). The proportion of patients who were culture confirmed remained stable at about 55% over the study period.

Trends in first line drug resistance

From 1998 to 2005 the percentage of cases resistant to any first line drug increased from 5.6% to 7.5% (with a peak of 7.9% in 2005). Isoniazid resistance increased from 5.0% to 7.2% in 2003 and remained stable thereafter. Multidrug resistance and rifampicin resistance increased from 0.8% to 0.9% and 1.0% to 1.2%, respectively. Resistance to pyrazinamide and ethambutol was low and no increases were noted (fig 1).

There was a significant linear trend of increasing isoniazid resistance apparent in univariable analyses, inside and outside London (1.05, 95% confidence interval 1.02 to 1.08, and 1.04, 1.01 to 1.07, respectively). Levels of multidrug resistance and rifampicin resistance also showed a significant linear trend over

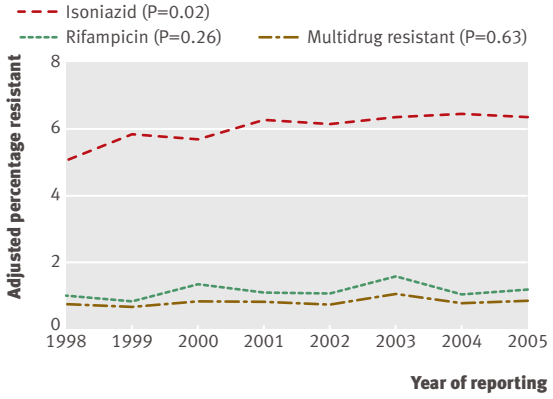

Fig 2 | Proportions of isoniazid, rifampicin, and multidrug resistance adjusted for age, place of birth, ethnic group, and previous diagnosis by year and significance of trend over time

the period (1.06, 1.00 to 1.12, and 1.06, 1.01 to 1.11, respectively).

Factors associated with trend

On multivariable analysis, only the rise in isoniazid resistance in London remained significant (1.04, 1.0 to 1.1). Specifically, the rise in isoniazid resistance outside London was no longer significant after adjustment for ethnicity, place of birth, or age (P for year=0.19, 0.15, and 0.11, respectively) (see full text on bmj.com). For multidrug resistance adjustment for previous diagnosis also had this effect (P for year=0.14) (fig 2).

In all models, younger age was significantly associated with resistance, while sex was not. Patients born outside the UK had a higher risk of drug resistance, including isoniazid resistance outside London, but a lower risk of isoniazid resistance in London. Compared with the white ethnic group, the risk of isoniazid resistance was significantly higher in black Caribbean patients in London (2.9, 2.1 to 4.1). Outside London, and for rifampicin resistance and multidrug resistance, the risk was higher in the black African, black other, Indian-Pakistani-Bangladeshi, and the Chinese ethnic groups (see full text and tables on bmj.com).

Patients with a previous diagnosis of tuberculosis were significantly more likely to be resistant in all models. Those with pulmonary disease were significantly more likely to be rifampicin resistant (see full text and tables on bmj.com).

Resistance to second and third line drugs among cases with multidrug resistant tuberculosis

Information on susceptibility to second and third line drugs was available for 99% of multidrug resistant cases reported in 2002-5. Resistance to second and third line drugs was low, with the exception of resistance to para-aminosalicylic acid (14%) and ethionamide (9%) (data available from authors). In 2003 one patient with no history of tuberculosis was found to have extensively drug resistant tuberculosis.

Molecular clusters of multidrug resistant tuberculosis

We had information on strain typing for 82% (66/81) of multidrug resistant cases reported in 2004-5. Six clusters affecting 19 patients were identified. The proportion clustered calculated with the n−1 method was 19.7% (see bmj.com).

DISCUSSION

The proportion of cases of tuberculosis resistant to isoniazid has increased during 1998-2005 in England, Wales, and Northern Ireland. This rise reflects the increasing proportion of patients with tuberculosis who are not born in the UK and of certain ethnic minority groups, as well as inadequate control of transmission in London. Levels of multidrug resistance and rifampicin resistance also showed a small increase. Levels of multidrug resistance in the UK are similar to those in other Western European countries.[11]

Strengths and limitations

In London, the prevalence of tuberculosis is high among homeless people and problem drug users, who might be disproportionately under-represented in surveillance data. Another limitation is the inability to adjust for the effects of some risk factors, such as coinfection with HIV or deprivation. Although the numbers of resistant cases were not large, potentially obscuring significant effects, the consistency of the results strengthens the conclusions. We needed to match two databases to combine data on drug susceptibility with demographic and clinical data, and we cannot exclude some inaccurate matches. Data on drug resistance were not available for 46% of reported cases (most were not culture confirmed), allowing scope for bias. This proportion remained stable over the study period and excluded patients were similar in terms of age, place of birth, and ethnic group, which were associated with both drug resistance and year of reporting.

Explanations for increases in drug resistance

The increase in isoniazid resistance outside London was related to increasing numbers of patients born outside the UK and also to changes in ethnic group and age. This increase is probably related to increasing numbers of drug resistant cases in people from sub-Saharan Africa and the Indian subcontinent, only few patients with drug resistant tuberculosis came from China and the former Soviet Union (see bmj.com). In London, the trend is probably related to the outbreak of isoniazid monoresistant tuberculosis, first noted in 1999.[15] Additional analysis of the effect of the outbreak on the trend in London confirmed this relation (see bmj.com). The same analysis also suggested that this outbreak accounts for the higher risk of isoniazid resistance in patients born in the UK and living in London. The outbreak is still continuing, suggesting that control measures are insufficient.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Antituberculosis drug resistance is increasing globally

Resistance to antituberculosis drugs in the UK remained stable between 1993 and 1999

Little information is available on potential transmission of multidrug resistant tuberculosis

WHAT THIS STUDY ADDS

From 1998 to 2005 the proportion of tuberculosis cases resistant to isoniazid increased in England

This increase was associated with increasing numbers of cases from sub-Saharan Africa and the Indian subcontinent, and inadequate control of transmission in London

Multidrug resistance increased only slightly and seems to be largely associated with problems in individual treatment, rather than transmission of infection

Rifampicin resistance and multidrug resistance also increased as a result of changes in demographic characteristics as well as clinical characteristics of patients. Nevertheless, the overall increase was small.

Transmission and management of multidrug resistance

The proportion of multidrug resistant cases resistant to second and third line drugs was low, suggesting that such patients are being managed effectively. The small numbers of cases tested meant we could not assess whether levels have increased over time.

Most cases of multidrug resistant tuberculosis are not caused by recent transmission in the UK. Among the 66 patients with strain typing information, 19 were part of six clusters. With allowance for one potential source case in each cluster, the estimated proportion of cases clustered was 20%. Cases that arise de novo, rather than as a result of recent transmission, suggest that failures in management of patients in the UK are contributing to the occurrence of multidrug resistance.

Conclusions

The increase in isoniazid resistance underlines the importance of using the recommended four drug course in the initial treatment phase for patients with tuberculosis[12] and of implementing measures to control the isoniazid resistant outbreak in London. The small increases in multidrug resistance and rifampicin resistance suggest a potential trend, which needs to be monitored.

We thank all staff of the microbiology laboratories involved in culture and testing of cultures of *M tuberculosis* isolates for their work and all tuberculosis nurses, chest physicians, and regional coordinators who submitted data to the enhanced tuberculosis surveillance system. We also thank Pam Sonnenberg for her extensive comments on the manuscript and Nick Andrews for statistical advice.

Contributors: See bmj.com.

Funding: None.

Competing interest: None declared.

Ethical approval: This study was carried out with national surveillance data. The Health Protection Agency has Patient Information Advisory Group approval to hold and analyse national surveillance data for public health purposes under Section 60 of the Health and Social Care Act 2001.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Ruddy MC, Davies AP, Yates MD, Yates S, Balasegaram S, Drabu Y, et al. Outbreak of isoniazid resistant tuberculosis in north London. *Thorax* 2004;59:279-85.
2 WHO. *Global tuberculosis control: surveillance, planning, financing*. Geneva: World Health Organization, 2007.
3 Djuretic T, Herbert J, Drobniewski F, Yates M, Smith EG, Magee JG, et al. Antibiotic resistant tuberculosis in the United Kingdom: 1993-1999. *Thorax* 2002;57:477-82.
4 Irish C, Herbert J, Bennett D, Gilham C, Drobniewski F, Williams R, et al. Database study of antibiotic resistant tuberculosis in the United Kingdom, 1994-6. *BMJ* 1999;318:497-8.
5 Kruijshaar ME, French CE, Anderson C, Abubakar I. *Tuberculosis in the UK. Annual report on tuberculosis surveillance and control in the UK 2007*. London: Health Protection Agency, 2007. www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1204100459636?p=1158945066450.
6 Rose AM, Watson JM, Graham C, Nunn AJ, Drobniewski F, Ormerod LP, et al. Tuberculosis at the end of the 20th century in England and Wales: results of a national survey in 1998. *Thorax* 2001;56:173-9.
7 Espinal MA, Laserson K, Camacho M, Fusheng Z, Kim SJ, Tlali RE, et al. Determinants of drug-resistant tuberculosis: analysis of 11 countries. *Int J Tuberc Lung Dis* 2001;5:887-93.
8 Faustini A, Hall AJ, Perucci CA. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. *Thorax* 2006;61:158-63.
9 Moniruzzaman A, Elwood RK, Schulzer M, FitzGerald JM. A population-based study of risk factors for drug-resistant TB in British Columbia. *Int J Tuberc Lung Dis* 2006;10:631-8.
10 Glynn JR, Vynnycky E, Fine PE. Influence of sampling on estimates of clustering and recent transmission of Mycobacterium tuberculosis derived from DNA fingerprinting techniques. *Am J Epidemiol* 1999;149:366-71.
11 EuroTB, National Coordinators for Tuberculosis Surveillance in the WHO European Region. *Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005*. Saint-Maurice, France: Institut de Veille Sanitaire, 2007.
12 National Collaborating Centre for Chronic Conditions. *Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control*. London: Royal College of Physicians, 2006.

Accepted: 26 March 2008

Crunching ice cube syndrome

The sound of crunching ice was obviously beginning to irritate the other members of my regular golfing foursome. Two were fellow doctors, but it was the retired garage proprietor who was getting most unsettled.

It had crept up on me imperceptibly, but now there was no mistaking that something odd was going on. Whatever soft drink I consumed had to be fully topped up with ice, while my regular lunchtime sherry was brimming over with small cubes. It was only when the craving began to afflict me at bedtime that I realised I had a problem.

My health otherwise seemed good, although I was tiring more in the garden—but, at almost 80 years old, what else could one expect? Only on the last day of the shooting season did I think I was really failing. Shooting at the end of January calls for a little more exercise than simply standing still while pheasants are driven to one, as happens earlier in the season. At the end of that day I had no chest pain, no marked breathlessness, just an overpowering feeling of extreme fatigue.

My garage proprietor friend slipped a small cutting from the *Daily Express* across the table to me as I sat crunching at the golf club. It stated: "although the exact reason is unclear, it is claimed crunching ice cubes may be a sign of iron deficiency anaemia."

"Old wives' tale," snorted my fellow golfing medics, but one bent over and squinted at my conjunctiva. Silence for a moment and then a gentle suggestion that my own doctor should have a look.

Next day I handed my general practitioner the cutting. I could sense the wheels turning as he surmised that I was really getting past it to take such things seriously. "Better do a blood test then. Phone up in a week, and you'll get the result."

Two days later the telephone rings, and a contrite voice tells me that my haemoglobin is 8.1 and the cells are microcytic and hypochromic.

I await gastroscopy and colonoscopy. Meanwhile a few weeks of ferrous sulphate has perked me up no end, and crunching ice now holds no attraction for me at all—but why? At the golf club we have welcomed a new consultant: he may have run a garage, but in our eyes he has fully qualified as a medic of distinction.

Francois L P Fouin retired GP, Aberdeen
flpf@stjulien.f9.co.uk