Tuberculosis in the UK, 1994: current issues and future trends

Tuberculosis, unfortunately, remains alive and well and continues to be a cause for concern. It raises a wide range of questions at the moment – for example, are the current arrangements for chest clinics and public health practices adequate for satisfactory disease control and how tight should these controls be? Who should treat tuberculosis and who should purchase that treatment? Is HIV-related tuberculosis a real threat in the UK and should we be concerned about the emergence of multidrug-resistant disease? Should patients who have or might have multidrug-resistant disease be compelled to accept treatment and isolation? What is the situation regarding BCG and appropriate screening of immigrants and refugees? None of these questions has a complete or satisfactory answer at the present time, so in this review we will address some of these issues in the light of current information.

The Joint Tuberculosis Committee of the British Thoracic Society will publish their updated code of practice for the control and prevention of tuberculosis in the next issue of *Thorax*. This document will define current practice on many of these issues on the basis of available information.

The rise in tuberculosis notifications in England and Wales over the last few years[1 2] has reopened debate on the effectiveness and adequacy of current control measures. Despite this recent modest rise in notifications against a trend of decline over the last 40 years, the UK remains a low prevalence country for tuberculosis, although there is a substantial geographical variation[3] with a number of inner city areas and towns having a prevalence several times the national average. In low prevalence countries such as the UK, case finding and effective chemotherapy remain the corner stone of tuberculosis control, whereas preventive measures (BCG) are of some benefit also. These control measures will now be discussed in the light of the situation within the UK at the moment.

Prevention

BCG VACCINATION

Routine unselected BCG vaccination of tuberculin negative school children was started in the 1950s and is still recommended for the 10–14 year age group by the Joint Committee on Vaccination and Immunisation of the UK[4] on the basis of uncertainties regarding the possibility of increased prevalence of tuberculosis due to HIV and other factors. BCG vaccination before contact with an infectious case has been shown to give 80% protection in the UK.[5] It is estimated that, at the moment, 4000 vaccinations are required to prevent a single case of tuberculosis. Before the recent rise in notifications it was estimated that there would only be 30 extra cases of tuberculosis per annum if the school BCG programme was stopped.[6] The future of the unselective schools' BCG programme will be decided in 1995 or 1996 when complete data analysis of the 1993 Communicable Disease Surveillance Centre, Department of Health, and British Thoracic Society notification survey becomes available. Of critical importance to that decision will be the 1993 notification rate in the white indigenous population aged 15–29, and whether this is continuing to fall when compared with 1988[7] and 1983.[8] Whatever the decision about the general unselective schools' programme in 1995, selective BCG for certain groups at particular risk will continue to be recommended. These groups are: neonates of Afro/Asian origin (neonatal vaccination is effective); tuberculin negative immigrants and refugees (children and young adults); tuberculin negative household contacts of pulmonary tuberculosis (children and young adults); tuberculin negative health care workers and others with contact with patients, prisoners or other high prevalence groups. Neonates from the Afro/Asian ethnic group have an increased incidence of tuberculosis even if born in the UK,[7 8] and neonatal BCG vaccination has been shown to have a 65% protection rate in case controlled studies.[9] Tuberculin negative children and young adult household contacts of pulmonary tuberculosis should be given BCG vaccination[10] as should similar tuberculin negative immigrants from high prevalence countries[10] of whom 30% are thus eligible for BCG.[11] Health care workers or other groups who have contact with patients, prisoners, or infected material from these groups should be protected by BCG vaccination unless they have a BCG scar or a positive tuberculin test. In schools children with Heaf tests grades 0–1 should be vaccinated; no vaccination is required for children with Heaf grade 2, whereas children with Heaf grades 3 and 4 should be referred for chest clinic assessment.

CHEMOPROPHYLAXIS

Children and young adults with strongly positive (grades 3 and 4) Heaf tests and no BCG history are at highest risk from developing clinical tuberculosis as this intensity of positive skin test is an indicator of previous infection. These children aged 0–15 years, whether found through contact tracing[10] or immigrant screening,[11] should be given chemoprophylaxis[10] which will significantly reduce the likelihood of subsequent clinical tuberculosis. Chemoprophylaxis should also be considered for young adults, particularly if recent tuberculin conversion has been demonstrated.[10] Either isoniazid for six months or rifampicin with isoniazid for three months are suitable.[12]

Case finding

General clinical awareness of the possibility of tuberculosis must be maintained, particularly in people from the Indian subcontinent who have an incidence of tuberculosis up to 25 times that of the white ethnic group,[7 8] people who may be infected with HIV, and the elderly who may have atypical presentations. Furthermore, active measures to detect clinical disease are required in household contacts, recent immigrants, and homeless people or those living in hostels.

HOUSEHOLD CONTACTS

Screening household contacts of cases of tuberculosis, particularly contacts of smear positive pulmonary disease, has a yield between 1%[13] and 8%[14] depending on district. Detailed recommendations on contact procedures were published in 1990[10] and will be discussed again in the updated recommendations of the Joint Tuberculosis Committee to be published next month.

RECENT IMMIGRANTS

Immigrants and refugees from high incidence areas of the world have a significant risk of developing tuberculosis, particularly during the first five years after entry to the UK.[15 16] The incidence of tuberculosis is particularly high in some groups – for example, in 1988 the crude incidence of tuberculosis was 135 per 100 000 in Indian, 101 per 100 000 in Pakistani/Bangladeshi, and 29 per 100 000 in AfroCaribbean groups, whereas it was only 4·7 per 100 000 amongst the white indigenous population.[16] Screening of immigrants in addition to detecting clinical disease also allows protection with BCG vaccination or chemoprophylaxis.[11] The Port of Arrival system for immigrants and refugees is recognised as being inefficient[11 17] and needs to be supplemented by good local arrangements for such groups.[10 11] This will depend on good liaison and appropriate funding of such liaison between the port of entry, the department of the local consultant in communicable diseases, and the district chest clinic. This aspect is unsatisfactory at the moment and requires consideration for the future in view of the continuing trend in refugees from armed conflict from various parts of the globe. Further work is required in this area and although next month's updated recommendations point the way forward, much detailed work and resource will be needed in coming years to control this important source which could lead to a general increase in prevalence of tuberculosis in the UK.

HOSTEL DWELLING/HOMELESS

As a result of increasing homelessness generally, it is important to be aware that such individuals have up to 100 times the incidence of tuberculosis when compared with the normal population.[18] Cases should be identified by active screening and prompt referral of such persons with respiratory symptoms to the local chest clinic. This is a difficult group to monitor and greater efforts and resources will be required to ensure adequate control of tuberculosis in this population which represents a potential pool of infection for the general population. The high incidence of vagrancy, alcoholism, drug addiction, and mental illness amongst this group renders them a substantial challenge for any disease control programme, usually requiring some form of supervised or directly observed therapy. This is another difficult area for tuberculosis control which will need much work. The new guidelines refer to it in general terms but more specific measures will be required.

Notification

All cases of tuberculosis should be notified to enable appropriate contact tracing and further case identification. Notification of all cases of tuberculosis diagnosed or suspected is a legal requirement. It is important, not just because of the need to maintain accurate epidemiological information and trends, but because notification is the only means whereby satisfactory contact tracing can be achieved. Failure to notify means failure to trace contacts which may result in further cases of failure to detect early clinical disease amongst such contacts and failure to offer protection from clinical disease by vaccination or appropriate use of chemoprophylaxis. Evidence of significant undernotification of 27% of bacteriologically and/or histologically proven tuberculosis, including 14% of sputum smear positive cases, has recently been reported.[19] The new guidelines usefully suggest that pathology and bacteriology laboratories could take an active role in the notification process to reduce undernotification.

Effective chemotherapy

Detailed guidelines and appropriate management and chemotherapy of tuberculosis have been published by the Joint Tuberculosis Committee.[12] The success of treatment depends on compliance, both by the physician in charge with recommended treatment guidelines and by the patient with the treatment given. Studies have shown that when treatment is not supervised by respiratory physicians there are significantly more treatment and prescription errors and hence unsatisfactory results.[20–22] Treatment of tuberculosis should therefore be supervised by a respiratory physician who should use standard treatment regimens and employ monthly compliance checks. This is emphasised in the new guidelines. Care of children with tuberculosis should be shared between paediatricians and respiratory physicians. Treatment generally should employ combination tablets to prevent accidental or deliberate monotherapy to minimise the risks of drug-resistant disease emerging.[23]

Compliance by doctors with standard treatment regimens has long been recognised as important to outcome[24] by the selection of the appropriate drugs at the correct dosage given for the appropriate length of time. This should now become the subject of standard national audit. Patient compliance is vital to successful outcome[25] and should be monitored monthly at least. The role of the tuberculosis nurse or health visitor in monitoring the treatment process is vital and should be in close liaison with the local chest clinic and supervising respiratory physician. The main cause of disease relapse is poor compliance, so regular assessment of compliance should include prescription checks, pill counts, and urine tests for rifampicin. If combination tablets containing rifampicin are being used then this is a marker for all the drugs. In national surveys about 10% of all tuberculosis patients are poorly compliant.[26] Those with proven non-compliance or those thought likely to be non-compliant must have treatment switched to full supervision.[10]

Standard treatment consists of rifampicin, isoniazid, and pyrazinamide for the first two months, followed by rifampicin and isoniazid for a further four months for respiratory and all non-respiratory tuberculosis (except for CNS tuberculosis where treatment should continue for 12 months altogether).[12] Ethambutol can be added to the initial treatment if local data suggest that there is a significant chance of isoniazid resistance in the patients' population group[12] or there is a history of previous treatment in a developing country.

Organisation of services

Close liaison between respiratory physicians and tuberculosis nurses or health visitors must be part of a detailed district policy.[10] This district policy should cover contact tracing arrangements, follow up, and compliance by patients, immigrant screening, and contingency plans for outbreaks. Responsibility for contact tracing and screening in England and Wales lies with the local consultant in communicable disease control. Close liaison with the local chest clinic is vital within an integrated policy at the local level. There should be a consultant respiratory physician in charge of the respiratory service to whom all staff are accountable for clinical matters. The Joint Tuberculosis Committee have set out criteria for nursing staff, the staffing level required being one whole time equivalent health visitor or nurse per 50 notifications per annum (with full clerical support)[27] to enable all measures to be in place that are required to maintain control of tuberculosis. To ensure that adequate resources and staff are available, purchasers and providers should agree contracts which specify control and treatment according to the guidelines

laid down by the Joint Tuberculosis Committee.[10 12 28] The revised guidelines to be published in *Thorax* next month will amplify the sections discussed here on prevention, notification, case finding, organisation of services, BCG, and chemoprophylaxis policies based on new information available since the previous guidelines of 1990.[10] The other potential problems relating to tuberculosis in the UK not covered by the new guidelines will now be discussed.

HIV and tuberculosis in the UK

The relationship between HIV and tuberculosis is well established.[29–31] Unlike the other opportunist infections that characterise HIV infection, tuberculosis is also infectious to normal individuals so that the prevalence of HIV disease may influence the prevalence of tuberculosis amongst the general population. Although tuberculosis in relation to HIV disease in the UK at the moment would not seem to be a major problem, there are no grounds for complacency in view of the situation in some African countries and some American cities. Clinical tuberculosis, when it complicates HIV disease, is largely due to reactivation[32] though primary infection and secondary exogenous infection undoubtedly occur also. In the UK only 5–6% of AIDS cases have tuberculosis during their clinical course.[33] The recent small rise in tuberculosis notifications seen generally in the UK is thought to be due to factors other than HIV[34] although tuberculosis may now also be increasing amongst HIV infected individuals.[35]

CLINICAL FEATURES

Tuberculosis can occur at any time in the course of HIV disease so that an HIV test should be considered in new cases of tuberculosis[30 36] in the UK. Tuberculosis in HIV infected individuals raises special diagnostic problems. The presentation may be atypical and extrapulmonary features may predominate, particularly when the CD4 count is low.[37] Typical radiographic features are frequently absent[37] and, because of the immunodeficiency, the tuberculin test is frequently negative in active disease.[38] Sputum is more frequently negative in HIV positive than in HIV negative individuals, again making diagnosis difficult.[33 39] Finally, mycobacteria may be seen in clinical specimens from HIV patients with symptoms and because of the high incidence of *Mycobacterium avian intracellulare* and other atypical mycobacteria in this group, confusion may arise as to the correct diagnosis before culture results become available.[40]

TREATMENT AND PREVENTION

Clinical response to standard treatment is normally good[41] but overall prognosis remains poor.[42] Standard six month regimens are recommended followed by isoniazid for life to prevent relapse in HIV positive cases; 18% have adverse drug reactions to standard treatment.[43] In the USA tuberculin testing is recommended for all HIV positive individuals and isoniazid prophylaxis for those with positive reactions (5 mm or greater to 5 tuberculin units) is recommended for at least one year.[32 42] Isoniazid prophylaxis in HIV disease has been shown to be effective[44] yet isoniazid prophylaxis in this group does contain some hazards which require consideration, and the risks and benefits remain to be determined.

Disseminated BCG has been reported following vaccination of AIDS patients.[45] BCG is therefore not recommended in HIV seropositive individuals. Furthermore, as much tuberculosis seen in HIV infected individuals is due to reactivation, BCG at the time of discovery of HIV status is unlikely to be helpful. Tuberculosis in HIV positive individuals is probably just as infectious as in HIV negative individuals[39 46] so contact tracing is extremely important amongst this group also. HIV seropositive contacts are probably more vulnerable to tuberculosis than HIV seronegative contacts.[47] Tuberculosis arising in HIV disease may be a hazard to health care workers. Multidrug-resistant disease has been transmitted to a health care worker.[48]

Tuberculosis and the inner city

Tuberculosis is to be found wherever there is homelessness, alcoholism, drug abuse, HIV infection, or immigrants from high prevalence areas. The tuberculosis notification rate is linked to poverty,[49] so the inner city environment offers opportunities for tuberculosis to spread amongst vulnerable groups. By contrast, in the suburbs, a high prevalence may be found where there is a high proportion of recent immigrants from areas with a high prevalence for tuberculosis. In the UK these features have long been recognised, resulting in an established and successful national tuberculosis control programme.

Recent experience in the USA: is there a warning for the UK?

Tuberculosis in the USA has increased since the mid 1980s and, unlike the UK, this has been attributed largely to HIV.[50] Inner city areas are predominantly affected due to large numbers of immigrants from high prevalence areas,[51] poor social conditions,[52 53] and the deterioration in the health care structure.[54] Overall incidence of tuberculosis in the USA is about 10 per 100 000 population, whereas in central Harlem and the lower east side of Manhattan the incidence is above 150 per 100 000.[55] A further problem in the USA is the appearance of multidrug-resistant strains of tuberculosis.[56] In a recent study from New York[51] of over 500 isolates 33% were resistant to one or more drugs, 26% were resistant to isoniazid, and 19% were resistant to isoniazid and rifampicin. Outbreaks of multidrug-resistant tuberculosis have been reported in hospitalised HIV patients.[58 59] The combination of multidrug-resistant tuberculosis and HIV infection has a very bad prognosis with a median survival of about two months.[57 60 61] Multidrug-resistant tuberculosis[62] can also occur in HIV seronegative individuals who also have a poor prognosis, with only half achieving negative sputum despite prolonged courses with the best available treatment.[63]

Recent experience from the USA has demonstrated again the way in which tuberculosis can spread rapidly within hospitals and prisons. The technique of restriction fragment length polymorphism has confirmed that the same organism may infect a number of individuals living in shelters for the homeless as well as in hospitals.[64–66] Tuberculin test surveys have also shown that transmission can occur in prisons between inmates and staff.[67]

It is now recognised that an important reason for the increase in tuberculosis in the USA, apart from HIV, has been reduced funding in the 1970s and 1980s for tuberculosis control. This lesson should be heeded by health care planners in the UK.[68 69] Good systems are in place for tuberculosis control in the UK, but they must be maintained in the new era of the NHS internal market. The gloomy lessons from the USA suggest that it must be made explicit to purchasers that the key to prevention of multidrug-resistant tuberculosis is good public health and chest clinic control measures combined with careful compliance to appropriate multiple drug regimens. Directly observed treatment is now recommended in the USA[70 71] and this, of course, is similar to the supervised approach which has been in the UK for many years. The ATS now

recognises the wisdom of combination tablet therapy to prevent inadvertent or intentional monotherapy.[68]

The Centers for Disease Control (CDC)[22] have provided guidance on the management of contacts exposed to multidrug-resistant tuberculosis. They suggest that, if in vitro sensitivity testing shows less than 100% isoniazid or rifampicin resistance, these drugs should still be included in the regimen on account of their overall bactericidal potency. The efficacy of alternative combination therapy for resistant disease remains undetermined by large controlled clinical studies. Suggested regimens include pyrazinamide with ethambutol or pyrazinamide with a fluoroquinolone (ciprofloxacin or ofloxacin). Appropriate duration of treatment also remains undetermined. The CDC suggests 6–12 months, but the safety of long term fluoroquinolones is uncertain. The lack of evidence for efficacy of these regimens raises problems for the contacts of cases infected with multidrug-resistant organisms. Generally such contacts should be followed for two years. If exposure is not regarded as high it is probably acceptable for HIV seronegative contacts to be followed up closely for two years rather than to be offered complex unproven potentially toxic drug combinations.

Further problems that the emergence of drug-resistant tuberculosis in the USA has raised are the ethical issues relating to the rights of society generally versus the rights of individuals with drug resistant tuberculosis when it comes to difficulties with compliance with treatment, unwillingness to be treated and the degree to which coercion is acceptable.[73]

The situation in the UK

Many of the procedures currently recommended in the USA have been in place in the UK for at least 60 years. Combination drug therapy with a single tablet is now routine and tuberculosis control measures are generally satisfactory. Multidrug-resistant disease is not yet a problem in the UK and the incidence of primary drug resistance remains low.[74] However, complacency would be misplaced, particularly in view of recent data showing that up to 27% of cases of tuberculosis may not be notified.[19] So far only small increases in tuberculosis associated with HIV have been reported. However, a particular problem is that notification rates on HIV seropositive patients may be as low as 30%.[75] There may be several reasons for this. Firstly, there are concerns regarding confidentiality. Secondly, health care provision for HIV seropositive individuals in the UK is variable and different groups of specialists may play a part. If a respiratory physician is not involved, then the normal notification and contact tracing procedures may be omitted. Thirdly, it may be difficult on clinical grounds – that is, before culture and sensitivity results become available – to distinguish between tuberculosis and infection with another mycobacterium such as *M avian intracellulare*. These factors are of concern in view of the danger of multidrug-resistant disease being introduced. Many of these problems would be helped by improved and speedier diagnosis. At the moment culture and determination of drug sensitivities take far too long. Techniques such as the polymerase chain reaction may allow rapid diagnosis in the future, and molecular techniques are beginning to unravel the mechanisms of drug resistance. In addition, techniques such as luciferase reporter phages may allow rapid determination of drug sensitivities in clinical samples allowing immediate and appropriate chemotherapy.[76]

In the UK, when drug-resistant tuberculosis does arise, treatment should only be carried out by a respiratory physician with experience of such cases. If isoniazid resistance is proven prior to treatment, a regimen of rifampicin, streptomycin, pyrazinamide, and ethambutol for two months, followed by rifampicin and ethambutol for a further seven months, has been shown to be effective.[77] If isoniazid resistance is detected after treatment has started, medication should be changed to rifampicin and ethambutol for 12 months with additional pyrazinamide for the first two months.[78]

Drug resistance to rifampicin and isoniazid in the UK is uncommon at the moment, and the level is not increasing.[75] The general principle of management is that at least three drugs to which the organisms are sensitive are continued until cultures become negative, and then a minimum of two drugs are continued for a further nine months. Such treatment needs to be planned on an individual basis, and to be closely monitored to prevent the emergence of further resistance.[12] Most cases of combined isoniazid/rifampicin resistance had received prior treatment outside the UK.[75] In the light of this information it may be wise to ensure that the initial treatment of reactivated tuberculosis previously treated abroad includes three drugs not previously given to the patient, as well as standard therapy, until the results of sensitivity tests are available.

Conclusion

This review has attempted to draw attention to some of the key issues surrounding tuberculosis today in the UK. Changes in disease prevalence, either generally or amongst special groups, the impact or otherwise of HIV, and the spectre of multidrug-resistant disease will determine our response in terms of BCG and treatment policy, but these trends will also stimulate a wider debate. If multidrug-resistant disease becomes a problem, should patients who might be infectious be constrained to accept treatment within the new NHS? How should tuberculosis services be provided and purchased and who should manage both the patients and the programme and so be held accountable? The Joint Tuberculosis Committee of the British Thoracic Society actively monitors all aspects of tuberculosis in the UK including epidemiological and drug resistance trends in conjunction with its formal links with the Department of Health, Communicable Disease Surveillance Centre, and Public Health Laboratory Service. It will continue to produce amended recommendations as circumstances change. Finally, to safeguard against the hazards that tuberculosis could bring, we believe that tuberculosis must remain firmly within the domain of the respiratory physician and that rigorous adherence to national guidelines should remain in place until some of the questions raised in this review are answered.

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