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Tuberculosis in Malta in the 21st century

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ABSTRACT: The World Health Organisation dedicated the 24th of March 1996 as World TB Day in a bid to promote its publicity campaign aimed at increasing awareness of the deteriorating situation as regards the treatment and control of tuberculosis.
Today's world population is about 5,700 million and TB is by far the major cause of death from infectious disease in persons over five years old. WHO estimates that one third of the world's population, that is, about 1,900 million are already infected and we know that approximately 10% of these will develop the disease. The real concern, however, is that current drugs may become useless. Indeed, it is estimated that more than 50 million people are infected with drug-resistant strains. On a global scale, the main cause of drug resistance is poorly managed TB control programs.

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Introduction

Dolin[1] estimated the rise in incidence over the present decade from 143/100,000 population in 1990, to 152/100,000 in 1995, to 163/100,000 in the year 2000. It may be worth noting that the increase between the years 1990 and 1995 is by 9/100,000 and between 1995 and 2,000 the increase is by 11/100,000. With each passing decade the increase is exponential. This data comes in part from a detailed analysis of notifications reaching WHO and from population surveys or estimates where no notifications were forthcoming. The study took into account changes in the size and age structure of the populations. The estimated mortality of 30 million over this decade takes into account the 2.9 million deaths expected from TB in AIDS patients. Globally, the incidence of AIDS has yet to peak and given its negative influence on tuberculosis, the incidence of the latter is also expected to continue to rise[2].

Against this background, it is timely to review the subject of tuberculosis in Malta. Today's control of TB in Malta is excellent thanks to the achievements of our predecessors. This is a good opportunity to highlight the historical landmarks, to assess current risks and to consider what might happen if we lose our current hold on the disease.

Recent History of TB control in Malta[3]

The first official notifications of TB began in 1920. In 1946, the health department established a tuberculosis service and its public health aspect was to be run by Dr Zammit Tabona. In the same year streptomycin became available but this was used initially to treat miliary and meningeal tuberculosis, until PAS became available a few years later and the two were increasingly used in combination to treat all forms of TB. As the rest of the western world embarked on a mass vaccination campaign with BCG, so did Malta. Supported by the International Commission for the Control of Tuberculosis, a Norwegian team came to Malta in 1949 to help set up mass tuberculin testing and a BCG campaign. In the first wave, between March and June of 1950, over 54 thousand people were tested and over 38 thousand vaccinated. The high tuberculin positive rate of 28.7% at that time reflects the percentage of the population already infected. The major turning point as elsewhere in the world came in 1952 with the availability of the highly effective drug isoniazid. During that year there were 64 artificial pneumothoraces induced, 15 thoracoplasties, 18 internal apical pneumolyses, 2 cistostomies and 2 phrenic nerve crushes. From then on, surgery for pulmonary TB declined rapidly.

The effects of TB control and treatment on the incidence of pulmonary TB in Malta are shown in Fig. 1. The trough during the war years possibly reflects a degree of under-reporting. The peak just after the war may have been due, partly, to a "catching-up" in reporting but probably also to a real rise in incidence as a result of a deterioration in social conditions during the war. It is worth noting that before the war, isolation of infectious cases and improving social conditions had already begun to reduce the incidence of pulmonary tuberculosis. The absolute figures of pulmonary tuberculosis, based on notifications between 1950 and 1995 show a steady decline to present day very low levels, with even the year to year variation diminishing (Fig. 2). The absolute number of deaths plotted on the same time scale (Fig. 3) show the dramatic effect of multiple drug treatment. Mortality was halved within two years. The steady fall in death rate thereafter mirrors the reduction in incidence and the effectiveness of treatment.

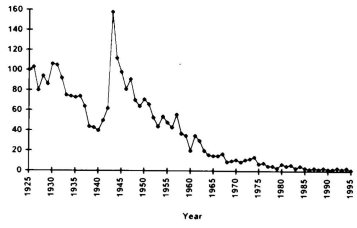

Fig. 1 - Crude incidence of Pulmonary Tuberculosis per 100,000 population in Malta 1925 - 1995

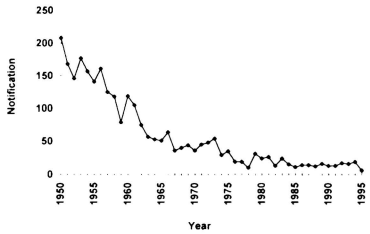

Fig. 2 - Pulmonary Tuberculosis in Malta - notifications 1950 - 1995

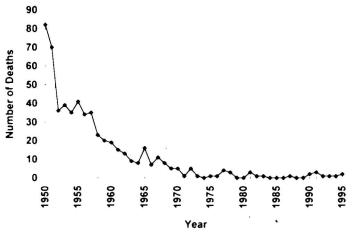

Fig. 3 - Deaths from Pulmonary Tuberculosis in Malta, 1950 - 1995

What is the risk of getting TB in Malta today?

Several factors may interact around an individual to place that person at a greater or lesser risk of contracting tuberculosis (Fig. 4). The first obvious one is the prevalence of the disease in the general population. A high prevalence will increase the chances of exposure to one or several cases, and repeatedly so during a lifetime. The prevalence of tuberculin positivity in the general population is a direct measure of exposure and infectivity[4,5]. A heavy exposure such as when in close contact with a family member or a colleague at work will greatly increase the risk of infection[6]. Once infected, there are other factors which may determine whether or not this will progress to produce the disease of tuberculosis. One factor is the infective dose. A very large number of inhaled organisms over a short period of time is more likely to result in disease than a small number[7]. The process may be accelerated in the case of very low or absent immunity or be greatly delayed or even halted in those with good immunity. Previous minor infections tend to favour the development and maintenance of immunity, but increasing age brings with it waning immunity and risk of breakdown of previously stable lesions as well as an increased risk of disease with each infecting dose[8]. Inadequate treatment saves lives but fails to cure. The result is that more persons with infection, over a longer time scale, are available in the community to spread the disease. There is no evidence that the virulence of the tubercle bacillus has changed significantly but it is known that resistance to treatment is the result of genetic alteration of the bacillus[9]. The single most important cause of reduced population immunity has been the spread of HIV[10]. This has had a dramatic effect on those populations where TB was common in the first place. It is believed that an improvement in the socio-economic status of the general population has helped to reduce the spread of the disease. But proof is difficult to come by. In present day circumstances, the risk of anyone getting TB in Malta must be very small. Since the number of cases of TB in Malta are so few, and the risk of getting TB is so low, why then are we concerned with what the World Health Organization is calling an epidemic? Is it really an epidemic?[11]

Is the global increase truly an epidemic?

This issue has been debated in the medical literature and there is general agreement that there is cause for concern[12-15]. In a schematic model of the evolution of an epidemic (Fig. 5), the time scale on the X axis will vary greatly according to the disease in question. For example, in the case of cholera this whole sequence can take place in months. In the case of TB it is probably

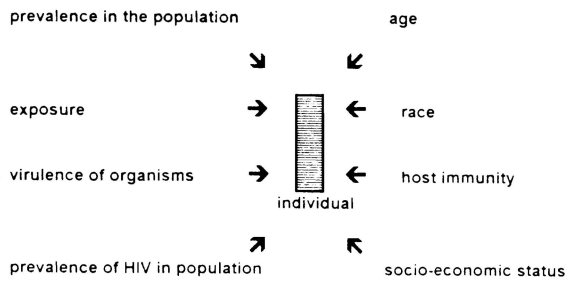

Fig. 4 - Factors influencing the risk of developing Tuberculosis

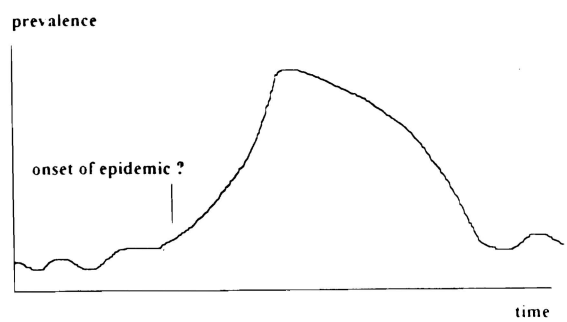

Fig. 5 - Schematic model of the evolution of an epidemic

best to interpret this axis in terms of decades at least. It is important to realise that decades will apply as much to the development of a TB epidemic as to its control. As a general rule, epidemics escalate more and more rapidly until a peak is reached. After a short plateau the number of cases falls, initially slowly, until a low baseline level of prevalence is again reached. Epidemics are generally triggered by factors which bring large numbers of non-immune people in close contact with a source of infection. In the absence of treatment, it is the gradual development of immunity in the general population which limits the epidemic[16]. With tuberculosis, the western world is at the lower end of the upslope. Many underdeveloped countries with a high incidence of TB were, ten to twenty years ago, on the down slope but the recent crisis has plateaued the fall or, in some cases, even reversed it[17]. Since the growth in incidence is exponential it would be foolish indeed to wait for even larger numbers to become infected before action is taken, particularly when we are seeing a loss of therapeutic efficacy of our drugs because of increasing resistance, falling health budgets, collapsing TB control programmes and, generally, loss of medical expertise in the condition[18]. The WHO believes that globally, the battle against tuberculosis is being lost.

Malta is fortunate not to have any of these problems at present. However, it must be remembered that the tubercle bacillus needs neither passport nor visa to enter Malta[19] And our nationals are not endowed with some special immunity against TB; so that they who spend time abroad in countries where TB is more prevalent are at increased risk.

Will it return?

This must remain an open question. Suffice it to say that many western nations with excellent records of TB control have seen a resurgence of the disease[20]. Two sub-populations have been particularly affected: the HIV positive / drug abusing population, and immigrants, whether as refugees or as temporary or permanent labour force[21-23]. Immigrants are more likely to have TB not only because many come from countries with higher prevalence rates, but also because their socio-economic status in the adopted country often puts them at greater risk of breakdown of their old infection, and their slow integration often delays their seeking medical help[24]. In Malta we are seeing greater numbers of refugees as well as children adopted from abroad. We do not feel these are a threat as they are well screened and, when necessary, treated. However, the same cannot be said for imported labour, which is also on the increase. There are loop-holes in the mechanisms for obtaining a work permit and for medical checks. Within this group, there have been cases of TB, one of which was isoniazid resistant. The matter has been taken up with the relevant authorities and we hope procedures will be reviewed and modified. It would take only one person with sputum positive pulmonary tuberculosis, infected with multi-drug resistant organisms to go undetected for a few months, to very seriously undermine our present safety. If TB did return, it is likely to return in small numbers initially and provided these are identified and the infecting bacilli are sensitive to first line drugs, the outbreak will be contained. If multi-drug resistant organisms become established, particularly in sub-populations who may be difficult to seek out and to monitor, then an outbreak will certainly be more difficult to contain. Less patients will be cured; there will be a need for isolation beds; health-care personnel will be at greater risk[25,26].

What impact will HIV have?

In 1984, the first reports emerged which showed that TB was more common in HIV positive individuals and this was mainly because of reactivation of old infection as their immunity waned[27]. These patients were treated with the usual unsupervised antituberculous chemotherapy regimen. This appeared to be as effective as in HIV negative cases[28]. However, these patients defaulted more frequently, both from follow-up and from taking their full course of prescribed treatment. They also lacked the immunity required to contain the disease and many returned to being sputum positive with high bacillary counts generally for longer periods because their organisms became resistant[29].

By 1989, reports of multi-drug resistant cases were published[30]. These patients had a median survival of only 2.1 months compared to 14.6 months if their organisms were fully susceptible to standard drugs. In 1992, reports emerged that nosocomial transmission of multidrug resistant strains was occurring[31]. This hospital cross infection was taking place from the patient with resistant bacilli to other patients receiving treatment for susceptible organisms, to previously uninfected persons and to health care personnel. Health care personnel have a 30% risk of becoming infected with multidrug resistant bacilli compared to a 2% risk if the organisms were sensitive[32-34]. This is because patients with sputum positive susceptible TB, when treated, are rendered non-infectious very quickly[7]. Their carers are therefore little exposed. Conversely, resistant bacilli remain in the sputum in large numbers, so that the duration and quantity of exposure is that much greater.

Freiden[35] illustrated the impact of AIDS and multi-drug resistant tuberculosis on mortality. Whereas young non-AIDS patients can expect almost 100% cure and survival, those with AIDS have a much higher mortality and those with AIDS and multi-drug resistance are nearly all dead within a year. There are now HIV positive individuals, infected with tubercle bacilli which are resistant to as many as seven different drugs[36]. The prevalence of TB in HIV positive persons is highly variable. For example it is in the region of 6% in the UK and 20-70% in some African countries[37]. The clinical and radiological presentations are often atypical and in western countries, the organism is frequently another species of Mycobacterium, commonly M. avium-intacellulare. The problems of TB in HIV positive patients are summarised in Table 1[38-40].

Although in Malta they are numerically small, persons who are HIV positive present a difficult problem. There is much secrecy surrounding their managment. Their assessment for TB, tuberculin status, prophylaxis and treatment is not in the hands of those doctors with experience in diagnosing and treating TB. The isolation requirements of HIV patients with tuberculosis and their treatment needs to be much more stringent than those for ordinary patients.

Table 1 - Tuberculosis in HIV positive persons

- Prevalence is very variable and presentation often atypical
- Organism is often an opportunistic Mycobacterium
- Tuberculin test and sputum smear are frequently negative
- Worse prognosis both for TB and HIV
- Need for life-long prophylaxis
- Drug resistance and cross infection more common

Should we modify our TB control policy?

Events have shown that the policy adopted by our predecessors was highly effective. This policy has been modified gradually over the years and today it does not differ significantly from the recommendations of the *British Thoracic Society*[41] and the *American Thoracic Society*[42]. The very low incidence of TB in our Islands is owing to the meticulous and persistent efforts of those who, firstly decided to establish a control programme and, secondly to those who worked solidly for many years to identify and treat infected individuals and screen their contacts. In this respect we must pay a special tribute to Dr A. Lanfranco who for over 40 years was largely responsible for the management of tuberculosis. He strove towards and achieved the excellent results we enjoy today. The value of diagnosing and supervising the treatment and contact screening of all patients with tuberculosis by specialists is well established. General physicians and surgeons should not, in a modern health care system, manage such patients on their own[43]. Particularly serious is the failure to notify cases or to institute adequate therapy. The solid foundations of a good control policy should not be undermined by unnecessary modernisation or by short-sighted cut-backs. On the contrary, any loop-holes which have evolved because of changes in our society should be tackled promptly.

But, if TB did return what can we expect?

Rapid diagnostic methods rely firstly upon efficient sample collection, either by sputum induction[44] or via the fiberoptic bronchoscope[45], followed by the examination of samples microscopically. This last remains essential and it is very quick and useful. Rapid culture techniques are also available. They confirm the diagnosis sooner and they are particularly useful to allow drug sensitivities to be given earlier[46,47]. For our small numbers and, so far, absence of drug resistance, these methods are not cost effective. DNA analysis using the polymerase chain reaction, once set up, is cheap to run. It can, in a few hours, confirm the presence or absence of mycobacterial DNA. It can also identify the very genetic status of the infecting bacillus and help substantially to identify the source of the infection[48-50]. But, in the context of public health medicine and the control of an epidemic, these techniques are, in a sense, closing the gate once the horse has bolted. Useful as they are for individual diagnosis or small scale epidemiological studies, it remains for effective public health policies and treatment strategies to control the disease in the general population.

The impact of drug resistance

In HIV-negative cases with susceptible bacilli, treatment with the standard three drug regimen is expected to result in only 0.5% treatment failure and a 9.2% risk of relapse. Resistance to one drug results in 11.4% treatment failure and a 24.4% risk of relapse. In years past, with non-HIV positive cases these effects of drug resistance though measurable, were manageable. The relapsers were re-treated with a new regimen, using some of the second line drugs[51]. With poor supervision, inadequate drug supplies, false economies where poor quality drugs or only two in combination were used, the frequency of drug resistance rose. With HIV, where bacillary populations in individual patients are high, noncompliance with treatment and loss to follow-up more frequent, resistance to several drugs simultaneously in the same patient has occurred more easily. Although patient noncompliance remains the main cause, the frequency of physician noncompliance must not be underestimated. The factors which interact to produce noncompliance have been extensively reviewed[52-56]. The causes of drug resistance are summarised in Table 2.

Table 2 - Causes of Drug Resistance

- Poor quality drugs
- Inadequate drug regimen
- Intermittent or inadequate drug supplies
- Doctor / patient error
- Physician noncompliance with recommended regimen
- Patient noncompliance with treatment

Treatment strategy

Directly observed treatment protocols have long been available. More recently, their advantages have been better appreciated, particularly in the context of patient groups like drug abusers, immigrants and the homeless, where failure of follow-up is more likely[57,58]. Directly observed treatment in short course has been shown to be cheaper and more efficacious. As shown in a study in Texas[59], acquired resistance fell seven fold, the rate of relapse fell to a quarter as did relapsers with multi-drug resistant organisms. Although this study can be criticised because the cohorts were studied in sequence and not simultaneously, it nevertheless, demonstrates the marked benefits of supervised treatment. The later cohort should, if anything, have been worse off, since homelessness, drug abuse, and prevalence of HIV and TB in the general population had all increased.

Although some new drug formulations and derivatives are available[60,61], no major new entity is envisaged or likely to be so in the near future. There is some hope in the use of drugs already available for other diseases, for example: amikacin, tetracycline, ofloxacin and clarithromycin. These drugs exhibit some efficacy against mycobacteria[62-67]. Their role is still being evaluated. Immunotherapy with killed Mycobacterium vaccae is effective[68]. Patients with tuberculosis who are vaccinated are more likely to heal and do so more quickly irrespective of their other treatment. This mode

of therapy is not in general use but it may have a role in those who are unable to receive first line drugs, for whatever reason. It is unlikely to be of benefit to immunosuppressed persons. These individuals, however, might benefit from the outcome of new research into auxotrophic strains of BCG[69]. (Auxotrophic strains are produced by the molecular biological technique of "insertional mutagenesis" to produce a strain which cannot survive without specific amino acids; in this case, methionine, leucine, isoleucine and valine.) Although these strains can revert gradually to the normal organism, the rate is extremely low. Thus the strain eventually dies in the host, so that should immunodeficiency progress, dissemination cannot take place. Yet, there appears to remain in the host enough immunity to allow the development of useful protection against infection.

Will surgery make a come-back?

Given that there are cases now which cannot be cured by drugs, this is a very pertinent question. Extensive disease which is caused either by multi-drug resistant organisms or extensive disease not responding to treatment has been effectively cured by surgical resection. Iseman[70] gives the following results of surgery, with or without chemotherapy: 83% long term cure if resectable; 11% long term morbidity (oxygen dependence); 2% mortality.

Conclusion

It would be wrong to paint too gloomy a picture. TB in the majority remains eminently curable. In a number of cases it presents a challenge to the clinician but it is still manageable. Only in very few instances is it untreatable. Our anxiety is that this very small group is increasing and we have no therapeutic armamentarium with which to control it. The need for strict public health surveillance and for adherence to proven treatment regimens is therefore of paramount importance. One cannot emphasize more strongly, the extreme importance of ensuring not only that the correct treatment is given, but also that cure with sterilization is actually achieved in all patients as rapidly as possible. Whilst there is certainly no cause for alarm in Malta, politicians who are in a position to act, and those medical authorities who formulate national health policies, should note the pitfalls and correct them before we, too, begin to climb the steep slope of an epidemic in our country.

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References

1. Dolin PJ, Raviglione MC, Kochi A. Global tuberculosis incidence and mortality during 1990-2000. Bull WHO 1994; 72: 213-200.
2. Nunn PP, Elliott AM, McAdam KPWJ. Impact of HIV on tuberculosis in developing countries. Thorax 1994; 49: 511-518.
3. Reports on the Health Conditions of the Maltese Islands, 1951-60. Department of Health, Malta.
4. Capewell S, Gordon LA. Tuberculin reactivity in a chest clinic: The effects of age and prior BCG vaccination. Br J Dis Chest 1986; 80: 37-44.
5. Sutherland I, Springett VH. Effectiveness of BCG vaccination in England and Wales in 1983. Tubercle 1987; 68: 81-92.
6. Riley RL, Moodie AS. Infectivity of patients with tuberculosis in inner city homes. Am Rev Respir Dis 1974; 110: 810-812.
7. Rouillon A, Perdrizet S, Parros R. Transmission of tubercle bacilli: the effects of chemotherapy. Tubercle 1976; 57: 275-299.
8. Isman MD. Tuberculosis in the young and the elderly. Chest 1995; 107(6): 1775.
9. Heym B, Honore N, Truffot-Pernot C, et al. Implications of multidrug resistance for the future of short course chemotherapy for tuberculosis: a molecular study. Lancet 1994; 344: 293-298.
10. Harries AD. Tuberculosis and human immunodeficiency virus infection in developing countries. Lancet 1990; 335: 387-389.
11. World Health Organisation. Tuberculosis notification update - July 1992. World Health Organisation, 1992.
12. Grzybowski S. Natural history of tuberculosis. Epidemiology. Bull Int Union Tuberc Lung Dis 1991;66(4): 193-194.
13. Davies PD. Is the increase in tuberculosis an epidemic? Br J Hosp Med 1993-94; 50(11): 632-634.
14. Kochi A. Tuberculosis: distribution, risk factors, mortality. Immunobiology 1994; 191(4-5): 325-336.
15. Nardini S, Donner CF, Rampulla C. Tuberculosis in the world: the pattern of the new epidemic. Monaldi Arch Chest Dis 1994; 94(3): 187-190.
16. Bates JH, Stead WW. The history of tuberculosis as a global epidemic. Med Clin North Am 1993; 77(6): 1205-1217.
17. Raviglione MC, Snider DE Jr, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. JAMA. 1995; 273(3): 220-226.
18. Brudney K, Dobkin J. Resurgent tuberculosis in New York City. Human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. Am Rev Respir Dis 1991; 144: 745-749.
19. Driver CR, Valway SE, Morgan WM, Onorato IM, Castro KG. Transmission ofMycobacterium tuberculosis associated with air travel. JAMA 1994; 272(13): 1031-1035.
20. Raviglione MC, Sudre P, Rieder HL et al. Secular trends of tuberculosis in Western Europe. Bull WHO 1993; 71(3/4): 297-306.
21. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 1989; 320: 545-550.
22. Porter J, Kessler C. Tuberculosis in refugees: a neglected dimension of the 'global epidemic of tuberculosis'. Trans R Soc Trop Med Hyg 1995; 89(3): 241-242.
23. Iseman MD. Immigrants and tuberculosis control. N Eng J Med 1995; 332(16): 1094-1095.
24. Ormerod LP. Tuberculosis screening and prevention in new immigrants 1983-88. Respir Med 1990; 84: 269-271.

25. Neville K, Bromberg A, Bromberg R, et al. The third epidemic - Multidrug resistant tuberculosis. Chest 1994; 105: 45-48.
26. Veen J. Drug resistant tuberculosis: back to sanatoria, surgery and cod-liver oil? Eur Respir J 1995; 8: 1073-1075.
27. Pitchenik AE, Cole C, Russel BW. Tuberculosis, atypical mycobacteriosis and the acquired immunodeficiency syndrome among Haitan and non-Haitan patients in South Florida. Ann Int Med 1984; 101: 641-645.
28. Brindle RJ, Nunn PP, Githui W, et al. Quantitative bacillary response to treatment in HIV-associated pulmonary tuberculosis. Am Rev Respir Dis 1993; 147: 958-961.
29. Fischl MA, Daikos GL, Uttamchandani RB et al. Clinical presentation and outcome of patients with HIV infection and tuberculosis caused by multiple-drug-resistant bacilli. Ann Intern Med 1992; 117: 184-190.
30. DiPerri G, Cruciani M, Danzi MC. Nosocomial epidemic of active tuberculosis among HIV-infected patients. Lancet 1989; ii: 1052-1054.
31. Pearson ML, Jereb JA, Friedan TR, et al. Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis: a risk to patients and health care workers. Ann Intern Med 1992; 117: 191-196.
32. Small PM, Shafer RW, Hopewell PC, et al. Exogenous reinfection with multidrug resistant Mycobacterium tuberculosis in patients with advanced HIV infection. N Engl J Med 1993; 328: 1137-1144.
33. Edlin BR, Tokars JI, Grieco MH, et al. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. N Engl J Med 1992; 326: 1514-1521.
34. Beck-Sague C, Dooley SW, Hutton MD, et al. Hospital outbreak of multidrug-resistant Mycobacterium tuberculosis infections: factors in transmission to staff and HIV-infected patients. JAMA 1992; 268: 1280-1286.
35. Frieden TR, Sterling T, Pablos-Mendez A, et al. The emergence of drug resistant tuberculosis in New York City. N Engl J Med 1993; 328: 521-526.
36. Ikeda RM, Birkhead GS, DiFerdinando GT, Jr, et al. Nosocomial tuberculosis: an outbreak of a strain resistant to seven drugs. Infect Control Hosp Epidemiol 1995; 16(3): 152-159.
37. Centers for Disease Control. Revision of the CDC case definition for acquired immune deficiency syndrome. MMWR 1987; 36(suppl.): 3-15.
38. Mitchell DM, Miller RF. New developments in the pulmonary diseases affecting HIV infected individuals. Thorax 1995; 50: 294-302.
39. Horsburgh CR, Havlik JA, Ellis DA, et al.. Survival of patients with AIDS and disseminated Mycobacterium avium complex infction with and without anti-mycobacterial chemotherapy. Am Rev Respir Dis 1991; 144: 557-559.
40. Pesanti EL. The negative tuberculin test. Tuberculin, HIV and Anergy Panels. Am J Respir Crit Care Med 1994; 149: 1699-1709.
41. Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: Code of Practice 1994. Thorax 1994; 49: 1193-1200.
42. A joint statement of the American Thoracic Society and the Centres for Disease Control and Prevention. Treatment of Tuberculosis and Tuberculosis Infection in Adults and Children. Am J Respir Crit Care Med 1994; 149: 1359-1374.
43. Wardman AG, Williams SE, Curzon PDG, Page RL, Cooke NJ. Tuberculosis: who should prescribe? BMJ 1982; 284: 569-571.
44. Parry CM, Kamoto O, Harries AD, et al. The use of sputum induction for establishing a diagnosis in patients with suspected pulmonary tuberculosis in Malawi. Tubercle Lung Dis 1995; 76(1): 72-76.
45. Baughman RP, Dohn MN, Louden RG, Frame PT. Bronchoscopy with bronchoalveolar lavage in tuberculosis and fungal infection. Chest 1991; 99(1): 92-97.
46. Snider DE Jr, Good RC, Kilburn JO, et al. Rapid drug-susceptibility testing of Mycobacterium tuberculosis. Am Rev Respir Dis 1981; 123: 402-406.
47. Jacobs WR Jr, Barletta RG, Udani R, et al. Rapid assessment of drug susceptibilities of Mycobacterium tuberculosis by means of luciferase reporter phages. Science 1993; 260: 819-822.
48. Small PM, Hopewell PC, Singh P, et al. The epidemiology of tuberculosis in San Francisco. A population-based study using conventional and molecular methods. N Engl J Med 1994; 330: 1703-1709.
49. Alland D, Kalkut GE, Moss AR et al. Transmission of tuberculosis in New York City. An analysis by DNA fingerprinting and conventional epidemiologic methods. N Engl J Med 1994; 330: 1710-1716.
50. Kent RJ, Uttley AHC, Stoker NG, Miller R, Pozniak AL. Transmission of tuberculosis in a British centre for patients infected with HIV. Lancet 1994; 309: 639-640.
51. Shimao T. Drug resistance in tuberculosis control. Tubercle 1987; 68(suppl 2): S5-18.
52. Fox W. Compliance of patients and physicians: experience and lessons from tuberculosis - I. BMJ 1983; 287: 33-35.
53. Fox W. Compliance of patients and physicians: experience and lessons from tuberculosis - II. BMJ 1983; 287: 101-105.
54. Wardman AG, Knox AJ, Muers MF, Page RL. Profiles of non-compliance with antituberculosis therapy. Br J Dis Chest 1988; 82: 285-289.
55. Ormerod LP, Prescott RJ. Inter-relations between relapses, drug regimens and compliance with treatment in tuberculosis. Respir Med 1991; 85: 239-242.
56. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis: common errors and their association with the acquisition of drug resistance. JAMA 1993; 270: 65-68.
57. Dutt AK, Moers D, Stead WW. Short-course chemotherapy for tuberculosis with mainly twice-weekly isoniazid and rifampin. Community physicians' seven-year experience with mainly outpatients. Am J Med 1984; 77: 233-242.
58. Cohn DL, Catlin BJ, Peterson KL, Judson FN, Sbarbaro JA. A 62-dose, 6-mo therapy for pulmonary and extrapulmonary tuberculosis. A twice-weekly, directly observed, and cost-effective regimen. Ann Intern Med 1990; 112: 407-415.
59. Weiss SE, Slocum PC, Blais FX. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N Engl J Med 1994; 330: 1179-1184.
60. Ellard GA, Ellard DR, Allen BW, et al. The bioavailability of isoniazid, rifampicin and pyrazinamide in two commercially available combined formulations designed for use in the short-course treatment of tuberculosis. Am Rev Respir Dis 1986; 133: 1076-1080.
61. Heifets LB. Lindholm-Levy PF, Iseman MD. Rifabutine: minimal inhibitory and bactericidal concentrations for Mycobacterium tuberculosis. Am Rev Respir Dis 1988; 137: 719-721.
62. Yew WW, Wong PC, Lee J, Chau CH. Ofloxacin and pulmonary tuberculosis. Chest 1994; 105: 1624.
63. Berning SE, Madsen L, Iseman MD, Peloquin CA. Long term safety of ofloxacin and ciprofloxacin in the treatment of mycobacterial infection. Am J Respir Crit

Care Med 1995; 151(6): 2006-2009.
64. Dautzenberg B, Truffot C, Legris S, et al.. Activity of Clarithromycin against Mycobacterium avium Infection in Patients with the Acquired Immune Deficiency Syndrome. Am Rev Respir Dis 1991; 144: 564-569.
65. Chiu J, Nussbaum J, Bozzette S, et al. Treatment of disseminated Mycobacterium avium complex infection in AIDS with amikacin, ethambutol, rifampin and ciprofloxacin. Ann Intern Med 1990; 113: 358-361.
66. Allen BW, Mitchinson DA, Chan YC, Yew WW, Allan WGL. Amikacin in the treatment of pulmonary tuberculosis. Tubercle 1983; 64: 111-118.
67. Heifets LB. Bacteriostatic and bactericidal activity of ciprofloxacin and ofloxacin against Mycobacterium tuberculosis and Mycobacterium avium complex. Tubercle 1987; 68: 267-276.
68. Onyebujoh PC, Abdulmumini T, Robinson S, Rook GA, Stanford JL. Immunotherapy with Mycobacterium vaccae as an addition to chemotherapy for the treatment of pulmonary tuberculosis under difficult conditions in Africa. Respir Med 1995; 89(3): 199-207.
69. Guleria I, Teitelbaum R, McAdam RA, et al. Auxotrophic vaccines for tuberculosis. Nature Medicine; 1996; 2 (3): 334-337.
70. Iseman MD. Treatment of multidrug resistant tuberculosis. N Eng J Med 1993; 329: 784-791.