

Zoonotic tuberculosis (*Mycobacterium bovis*): Memorandum from a WHO meeting (with the participation of FAO)*

In view of the considerable and continuing public health significance of Mycobacterium bovis infection in humans and animals, WHO convened a meeting on zoonotic tuberculosis in Geneva in November 1993. The participants at the meeting reviewed the human and animal tuberculosis situation worldwide, discussed the zoonotic aspects of M. bovis infection in United Republic of Tanzania and Zambia, exchanged views on methodologies in epidemiology, immunology and molecular biology, and identified areas for further research and intersectoral collaboration. A project protocol to investigate the zoonotic aspects of bovine tuberculosis was elaborated by the group and included in their report. This Memorandum is a summary of the full report of the meeting.

Introduction

Animal tuberculosis

In developing countries, especially in Africa where *Mycobacterium bovis* infection is present in animal species, there is a substantial lack of knowledge of the distribution, epidemiological patterns and zoonotic implications of this important zoonosis. Thus, there is a need for improvement, taking also into account the veterinary public health aspects of human *M. bovis* infection, particularly in populations at risk. Some data, however, exist on disease occurrence and control in certain African countries (1, 8).^a

Ten out of 56 African countries did not report any bovine tuberculosis (BTB), or have no available information on this disease. Kenya has never reported BTB, and Namibia recorded its last cases in bovine and swine populations in 1985 and 1965 respectively. Forty-four African countries officially

recognize the presence of BTB in their animal population (1, 8).

Out of 56 countries, 30 apply some control measures, in 16 of which bovine tuberculosis is a notifiable disease. However, only 6 countries out of these 16 also carry out a testing and stamping-out policy (1, 8). On the other hand, South Africa and Tunisia alone have declared a national control programme, while Morocco and Mozambique have control policies for intensive dairy farming.

Of the total African cattle and dairy populations, more than 50% are found in countries without any control measures for BTB, and only approximately 10% are found in countries where BTB is a notifiable disease and where testing and stamping-out are also applied. Thus, approximately 90% of cattle and dairy cow populations in Africa are either only partly controlled for BTB or not controlled at all. It is also possible to estimate that approximately 90% of the human population lives in countries where cattle and dairy cows undergo no control or only limited control for bovine tuberculosis (1).

Update on human tuberculosis and trends

Human tuberculosis is still the single greatest cause of human morbidity and mortality in many developing countries. *M. tuberculosis* is the most frequent cause of human tuberculosis, but some cases are caused by *M. bovis*. The forecast of tuberculosis morbidity and mortality up to the year 2000 is as follows. During the decade 1990–99 an estimated 88.2 million new cases of tuberculosis will occur in the world, of which 8 million will be attributable to HIV infection; 30 million are predicted to die of tuberculosis during this decade, including 2.9 million tuberculosis deaths in those also infected with HIV. The number of new tuberculosis cases occurring each year is predicted to increase from 7.5 million (143

* This Memorandum is a summary of the Report of the WHO Meeting on Zoonotic Tuberculosis (*Mycobacterium bovis*) with the participation of FAO (document WHO/CDS/VPH/93.130). The participants at the meeting, which was held in Geneva on 15 November 1993, were Dr A. Cook, Lusaka, Zambia; Dr C. Daborn, Edinburgh, Scotland; Dr J.M. Grange (Chairman), London, England; Dr J. Haagsma, Lelystad, Netherlands; Dr J.M. Sharp, Edinburgh, Scotland; Dr C.O. Thoen, Ames, Iowa, USA; and Dr A. Benkirane, Food and Agriculture Organization, Rome, Italy. WHO Secretariat: Dr O. Cosivi (Secretary), Dr T. Fujikura, Dr M. Kaplan, Dr F.-X. Meslin, Dr M. Raviglione, and Dr K. Stöhr.

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^a Food and Agriculture Organization. *Zoonotic diseases in the Near East region*. FAO Regional Office for the Near East, Cairo, 1993.

cases per 100 000) in 1990 to 8.8 million (152 per 100 000) by 1995 and 10.2 million (163 per 100 000) by 2000. In 1990, 2.5 million persons were estimated to have died of tuberculosis. Assuming that availability of treatment remains at its 1990 level, it is predicted that 3 million tuberculosis deaths will occur annually by 1995 and 3.5 million annually by 2000. Demographic factors, such as population growth and changes in the age structure of populations will account for 79.5% of the predicted increases in new cases. Age-specific incidence rates in sub-Saharan Africa are increasing due to the HIV epidemic and will account for the remaining 20.5% of the forecast increase in new cases.

Zoonotic aspects of *M. bovis* infection

Many questions still surround the nature and epidemiology of human tuberculosis due to *M. bovis* (13). The disease is transmissible from cattle to humans directly by the aerogenous route and indirectly by consumption of milk. It is not clear, however, whether progression from infection to overt disease occurs as readily as in the case of *M. tuberculosis*. Epidemiological studies indicate that people infected by *M. bovis* are less likely to develop post-primary disease later in life than those infected by *M. tuberculosis*, but it is not clear whether this is the result of differences in the predominant route of infection or to differences in host susceptibility.

Primary human disease due to *M. bovis* is very rare in developed countries where bovine tuberculosis has been eradicated but the transmissible post-primary (reactivation) form of the disease is still encountered, almost all cases being reported in persons born before the bovine eradication schemes were completed. Almost all cases of primary human disease due to *M. bovis* are non-pulmonary (farmers, however, were more likely to develop primary pulmonary disease than town-dwellers), but about half the cases of post-primary disease involve the lung. This raises the possibility of human-to-human transmission of tuberculosis due to *M. bovis*; evidence of this occurrence is limited and anecdotal owing to the lack of typing schemes, until the very recent introduction of DNA fingerprinting, for tubercle bacilli and the long interval between infection and development of overt primary or post-primary disease. Any immune factors preventing progression of infection by *M. bovis*, whether of animal or human origin, to overt human disease, could well be suppressed by co-infection by HIV. Cases of HIV-related human tuberculosis due to *M. bovis* have been reported in England (9), France (10), and the USA (southern California) (11). The possibility that HIV infection may lead to a perpetuating cycle of transmission of

animal-to-human, human-to-human and human-to-animal thus requires careful consideration. Human-to-human transmission of disease due to *M. bovis* in HIV-positive persons has recently been confirmed. A single case in a Paris hospital, with a strain of *M. bovis* resistant to many antituberculosis drugs, was the source of infection in five patients, the disease occurring 1 to 10 months after infection (12).

WHO-coordinated activities

WHO, through its Veterinary Public Health unit (VPH), is particularly interested in the public health significance of *M. bovis* infection in humans and animals, as well as the safety of food of animal origin with regard to contamination by *M. bovis*. The efforts of VPH have been continuing in (i) the worldwide surveillance of animal tuberculosis, jointly with relevant services in the Food and Agriculture Organization (FAO) and the Office international des Epizooties (OIE) (1), and (ii) research in epidemiology, standardization of diagnostic methods and reagents, and measures for prevention/control, including food hygiene aspects, with special references to intersectoral collaboration (2-7).^{b, c, d} In 1992 WHO organized and coordinated a working group meeting on the epidemiology, public health aspects and control of animal tuberculosis and on research.^e Another meeting was convened in November 1993 in order to (1) review the human and animal tuberculosis situation worldwide; (2) discuss the zoonotic aspects of *M. bovis* infection with the Overseas Development Administration teams working in the United Republic of Tanzania and in Zambia, and promote their projects as well as international cooperation and support; (3) exchange views on methodologies in epidemiology, immunology and molecular biology for project support and cooperation with the WHO-coordinated working group; and (4) identify areas for further research and facilitate intersectoral collaboration between medical and veterinary professionals on zoonotic tuberculosis. The results and recommendations are summarized below.

^b *Guide for the bovine tuberculosis projects*. PAHO/WHO/Pan American Zoonoses Center, Technical Note No 15/Rev. 1, 1989.

^c **PAHO/WHO**. Strategy and plan of action for the eradication of bovine tuberculosis in the Americas. In: *VII Inter-American Meeting, at Ministerial Level, on Animal Health*. Washington DC, USA, 30 April - 2 May 1993.

^d **PAHO/WHO**. Plan of action for the eradication of bovine tuberculosis in the Americas. Phase I. In: *VIII Inter-American Meeting, at Ministerial Level, on Animal Health*. Washington DC, USA, 27-29 April 1993.

^e *Report of the WHO Working Group Meeting on Animal Tuberculosis*. Cairo, Egypt, 27 April 1992 (unpublished document WHO/CDS/VPH/92.112).

Research activities

Recent advances in tuberculosis control

A number of new diagnostic tests have become available and are briefly described below. However, the simple and practical tuberculin test remains very important because the new tests have not yet been fully evaluated.

(i) *Lymphocyte proliferation assays*. This type of *in vivo* assay detects cellular reactivity to tuberculin PPD antigens in whole-blood samples. These assays are of scientific interest, but are not used for routine diagnosis because they are time-consuming with rather complicated logistic and laboratory procedures.

(ii) *γ-Interferon test*. This test measures the release of a lymphokine in a whole-blood culture system. The advantage over the skin test is that the animals only need to be captured once, but the serious disadvantages are the high costs and the fact that processing of the blood samples has to be commenced within 8 hours of collection.

(iii) *ELISA*. Enzyme-linked immunosorbent assay appears to be complementary rather than an alternative to tests based on cellular immunity, and may be very helpful in anergic cattle. Specificity and sensitivity both need to be improved. An advantage of the ELISA is its simplicity.

(iv) *DNA probe/PCR technique*. The DNA oligonucleotide probe/PCR (polymerase chain reaction) assay can, in principle, be used to detect *M. bovis* DNA in sputum, blood, nasal swabs and other tissues. Unfortunately, the available PCR primers do not discriminate between *M. tuberculosis* and *M. bovis*, and sensitivity and specificity need further evaluation. The DNA probe/PCR technique can also be used to differentiate between mycobacterial isolates. A novel method for examining clinical specimens is based on infection of viable *M. tuberculosis* by a phage carrying the luciferase gene expressed by a mycobacterial promoter. Obvious advantages of this method over the PCR are its simplicity and the absence of the notorious problem of false positivity caused by cross-contamination with previously amplified DNA.

(v) *DNA-fingerprinting* (restriction fragment length polymorphism, RFLP). This can be a very useful tool in the epidemiology of tuberculosis, to study the transmission of *M. tuberculosis* and *M. bovis* between animals and humans.

In general, it is advisable to rely on established techniques because the modern techniques, in particular PCR, need further evaluation in order to avoid false-negative and false-positive results.

Overseas Development Administration's Tanzanian project

The Research Programme on Bovine Tuberculosis in the Tropics, funded by an ODA research grant for a three-year term, commenced in January 1993. The programme is broadly divided into two components: a field epidemiological component based at the Veterinary Faculty, Sokoine University of Agriculture, Morogoro, Tanzania, and a laboratory component, based at the Moredun Research Institute, Edinburgh, Scotland, aimed at developing new molecular tests to diagnose and discriminate between members of the *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum* and *M. microti*). The activities are summarized below.

(1) *Field epidemiological component, Sokoine University of Agriculture (SUA)*. The infrastructure for culturing and for differentiating between members of the *M. tuberculosis* complex have been established at the SUA Veterinary Faculty. Samples from bovine and human tuberculosis cases are being collected for culture in the newly established SUA facility and for analysis by molecular tests in Edinburgh. Preliminary work on tuberculin test validation under local conditions and comparison with the ELISA and γ -interferon tests has been undertaken, and the results are being analysed. A pilot field study on the performance of tuberculin test complemented by an ELISA in the southern highlands area of Tanzania will be continued until the end of 1994.

The main aims of this component of the project are: (a) to assess the zoonotic importance of *M. bovis* in Tanzania, (b) to undertake epidemiological studies to determine the distribution, prevalence and modes of transmission of *M. bovis* in Tanzania, and (c) the production, on the basis of the results obtained, of training guidelines for staff and farms on the control of bovine tuberculosis in cattle in Tanzania and the prevention of zoonotic transmission.

Future activities will include (i) collection of human tuberculosis samples from various district hospitals with the assistance of the National Tuberculosis and Leprosy Programme, (ii) validation of the tuberculin test sensitivity and specificity using animals from pastoral people and dairy animals from smallholding farms of the region, and comparison with ELISA and γ -interferon tests, and (iii) epidemiological studies by tracing patients infected with *M. bovis* to assess possible sources and routes of infection, and risk factors. In areas with significant bovine tuberculosis, the possibility of zoonotic transmission will be investigated.

(2) *Laboratory component, Moredun Research Institute (MRI)*. Published information on molecular

test development has indicated that organisms containing the insertion sequences IS986 and IS1081 belong to the *M. tuberculosis* complex and those containing mtb 40 are *M. tuberculosis*. PCR assays based on these sequences have been developed to run simultaneously in one tube. The ability of these PCRs to detect members of the *M. tuberculosis* complex in necropsy samples will build on MRI's experience and success with a simple and inexpensive technique to extract mycobacteria from tissues and prepare DNA for subsequent PCRs. Strain differentiation in epidemiological studies will be obtained by standard RFLP techniques, as well as pulse field electrophoresis and PCR. At least one *M. bovis*-specific protein (mtb 70) has already been described although the gene is also present in the *M. tuberculosis* complex. New approaches to detect further specific proteins and genes, and to discriminate within the *M. tuberculosis* complex will be based on, and will depend on, the ability of MRI to use molecular techniques to exploit the biochemical features that are currently being used to speciate within the *M. tuberculosis* complex.

Overseas Development Administration's Zambian project

This study was carried out by the Department of Clinical Studies, London School of Hygiene and Tropical Medicine, London, in collaboration with the University Teaching Hospital and the Veterinary Faculty of the University of Lusaka, Zambia. The study established the prevalence of bovine tuberculosis and investigated its association with human tuberculosis (HTB) in the Monze district of Zambia. Rural households were selected at random from an existing sampling frame of 1720 such households. Participating householders completed questionnaires and presented their animals for the comparative tuberculin test. Data were analysed using the Epi-Info program.

The survey of the 176 randomly selected rural households revealed that 68% owned cattle. A total of 103 herds, comprising 2226 cattle, were subjected to the comparative tuberculin test; 165 cattle (7.4%) from 33 herds (herd prevalence, 32%) gave positive reactions.

Pregnant cows, animals in better body condition, and older animals (up to the age of 6 years) were more likely to be positive reactors. There was a positive correlation between herd size and within-herd prevalence of reactors. Owners of herds containing positive cattle were more likely to report that their cattle coughed. Prevalence of reactors varied significantly with area. The data suggested that contact with wild animals might be associated with presence of tuberculin-positive cattle. The local red lechwe

(*Kobus lechwe kafuensis*) population is known to be endemically infected with tuberculosis. Increased herd mortality and a shared watering point might also be associated with presence of reactors in a herd.

Ten households out of 176 (5.7%) reported a human tuberculosis case within the previous 12 months. These households were approximately 7 times more likely to own herds containing tuberculin-positive cattle (odds ratio = 7.6; $P = 0.004$). This could be due to transmission of tuberculosis between people and cattle, to transient sensitivity to tuberculin in cattle exposed to a human case, or to a coincidental environmental factor favouring both human clinical tuberculosis and bovine tuberculin sensitivity.

The results of this study demonstrated a relatively high prevalence of tuberculin-positive cattle and of herds containing such cattle within Monze District. The study also indicated that there is a potential link between animal and human tuberculosis in a traditional African rural environment. The significant association between the presence of a household case of tuberculosis and of tuberculin-positive animals in the contact herd is of both medical and veterinary concern. Further research is planned to (i) validate the bovine tuberculin test under local conditions; (ii) compare RFLP patterns from mycobacteria isolated from human cases, cattle and lechwe; and (iii) investigate the association between tuberculin-positive cattle and human clinical tuberculosis by means of a case-control study.

Discussion

The discussions were structured under five topics.

International cooperation, funding and training.

Informed comment on the zoonotic importance of *M. bovis*, particularly in developing countries, is hampered by two principal deficiencies: firstly, a lack of information on the distribution and prevalence of infection and disease due to *M. bovis* in both animals and humans, and secondly a lack of resources, primarily funds, for countries to investigate and provide such information. The current attention being focused on human tuberculosis, particularly in developing countries, and its association with HIV/AIDS should provide an improved prospect of attracting funds for *M. bovis* research. There is a need to collect hard evidence concerning the zoonotic importance of *M. bovis* in the current human tuberculosis epidemic in developing countries. The first priority is to set in motion a programme to address this question.

Epidemiology and surveillance. It has been recognized that bovine tuberculosis may have a number of

significantly different epidemiological patterns in developing countries and, although much can be learnt from the European experience of the 1930s and 1940s, it is important to conduct specific in-country investigations into the circumstances in which *M. bovis* is of zoonotic importance and the underlying mechanisms of transmission. Well-planned epidemiological studies are required to provide quality information on which to base research priorities and develop strategic cost-efficient control programmes.

Control. The test-and-slaughter policy is likely to remain the mainstay of the bovine tuberculosis control programme in any given country, though it has been recognized that this may not be a universally practicable policy for all developing countries or for the whole cattle population in any one developing country. It is possible that some countries need to adopt a modified form of the test-and-slaughter policy, perhaps introduced on a stepwise basis with the use of interim measures such as segregation and phased slaughter of reactors. An FAO/WHO publication previously elaborated on the control of bovine tuberculosis in line with these principles (3). The role of vaccination and chemotherapy in controlling bovine tuberculosis was discussed at length, with a spectrum of views for and against. It was recognized that the available information was insufficient to permit the endorsement of any general adoption of either approach and that small-scale controlled pilot trials might be the way forward in the first instance, particularly in situations where the test-and-slaughter policy was totally impracticable. There is an urgent need for further research on the performance of diagnostic tests to be used in control programmes and also for the questions of vaccination and chemotherapy to be addressed.

Diagnosis. New diagnostic tests may provide the key to achieving a more critical interpretation of a given animal tuberculosis status. The genetics of African cattle immune systems, and their environment, may differ from that of *Bos taurus* breeds on which most test evaluation has been based. It is necessary to validate the performance of diagnostic methods (tuberculin test, culture and species discrimination, post-mortem examination, ELISA, γ -interferon assay, etc.) under the conditions of the country in which the tests are to be used. The importance of tests that will discriminate between strains within the *M. tuberculosis* complex was noted. The potential contribution that molecular techniques, such as the PCR and RFLP, could make to epidemiological studies and investigation of sources of infection was discussed and recognized. The importance of reliable culture

facilities and diagnostic tests for investigating the epidemiology, zoonotic importance and control of bovine tuberculosis is axiomatic. Conventional and new tests require evaluation under the conditions in which they are to be used. Current work in the tropics on this aspect is therefore recommended and expected to point the way for future test development.

Human aspects. It is very important to have collaboration between medical and veterinary programmes at local, national and international levels. The successful role of the IUATLD (International Union against Tuberculosis and Lung Disease) in promoting this approach was recognized. There is a need for both medical and veterinary expert appraisal of the zoonotic importance of *M. bovis* for a given developing country. Effective collaboration between medical and veterinary personnel is essential for the investigation of the zoonotic importance of *M. bovis*.

Recommendations

Cooperation/collaboration. In view of the recent increasing health problems due to tuberculosis in the population at large the world over, the group urged cooperation in controlling tuberculosis with special attention to zoonotic aspects. In this context, inter-sectoral cooperation between medical, public health, veterinary, agricultural, environmental, food safety, nature conservation, anthropological and many other related sectors should be promoted for controlling tuberculosis in humans and animals, particularly in Africa. In-country cooperation and close collaboration between medical and veterinary personnel for effective and cost-efficiency investigation, as well as for sharing of mycobacteria cultures and isolation facilities, should be established or strengthened.

Training. Training at all levels is still requested for the implementation of a programme on bovine tuberculosis (surveillance, investigation, diagnosis and control). It will be a primary requirement to ensure full and informed participation of local personnel in any programme. The Centre for Tropical Veterinary Medicine, University of Edinburgh, Scotland, should be considered for designation as a WHO Collaborating Centre for research and training in the public health aspects of bovine tuberculosis.

Research. The group strongly recommended the promotion of research cooperation and coordination in the following areas.

(i) *Epidemiology and surveillance.* If a given country or area lacks a BTB surveillance programme and/or there are no data on the epidemiological situa-

tion at national/regional levels, the initial work should focus on gathering information from such existing sources as hospitals, laboratories and abattoirs. It was emphasised, however, that there are likely to be inherent deficiencies in such sources of data. Any plan to investigate bovine tuberculosis should, where possible, include such aspects as social anthropology, environmental factors, genetic differences and influences, and most importantly, the impact of the HIV/AIDS epidemic. There is a need to identify local risk factors for zoonotic tuberculosis in order to determine populations at risk and to implement appropriate control measures.

(ii) *Socioeconomic studies.* Research on health and agricultural systems at national/regional levels in controlling tuberculosis with zoonotic aspects and in examining the cost-effectiveness of any proposed control programme was also strongly recommended. The test-and-slaughter policy should remain the central policy for the control of bovine tuberculosis in developing countries but modification of the practice may be necessary in certain situations.

(iii) *Diagnosis and control.* There is an urgent need for further research on the performance of diagnostic tests to be used in control programmes and also for the questions of vaccination and chemotherapy to be addressed. Applied research into diagnosis and control (including vaccination and chemotherapy) of bovine tuberculosis should be strengthened. It is necessary to validate the performance of applied diagnostic methods under the conditions of the country in which the tests are to be used. Further trials, under tropical conditions, with the new serological (ELISA) and cytokine (γ -interferon) approaches to the diagnosis of bovine tuberculosis are needed. Work needs to be continued to identify specific antigens for detection as well as diagnostic and possible immunogenic purposes. There is a strong need to distinguish between those diagnostic tests that work in the tropics and those requiring further research and development. Thus, investigation of bovine tuberculosis should have a strong diagnostic test evaluation and development component. Standardization, both within and between countries, of laboratory culture techniques for mycobacteria and the species discrimination tests should be adopted if true comparisons of results are to be made. The development and supply of kits may be one approach for diagnosis of bovine tuberculosis. This would assist where supplies of reagents may be uncertain. The approach of the International Atomic Energy Agency in Vienna in developing such kits for ELISA tests was seen as a notable example. The importance of tests that will discriminate between strains of *M. bovis* was noted. The potential contribution of

molecular techniques to identify species-specific genes and strain markers was discussed and recognized. These include the PCR and RFLP, which could promote further epidemiological studies and investigation of sources of infection.

(iv) *Immunity and natural resistance.* The question of the immune response to tuberculin and other diagnostic antigens should be examined with a view to establishing all the possible interpretations that reactivity implies. This study should take place on different cattle breeds (including both *B. taurus* and *B. indicus*) in a range of locations in the tropics and under various systems of management. It will be important to determine if a percentage of reactors are displaying immune competence and not solely a status of active or contained infection. A fundamental question to ask is whether natural resistance to bovine tuberculosis occurs and, if so, is it influenced by breed?

Coordination. International cooperation must be sought with the support and involvement of the international agencies including FAO, IUATLD, OIE, UNDP and WHO. There is a need to clarify the relationship and strengthen existing links between the representative groups (i.e., IUATLD and WHO) and support agencies (i.e., the European Union and FAO) to provide clear guidelines for maximizing international cooperation. It is important to establish a representative and effective voice on the zoonotic aspects of *M. bovis*, to express the concerns and needs, to set work targets, and to monitor progress.

Reference laboratory. A general policy on access to reference strains of mycobacteria was urgently needed. The problem of some laboratories reporting on a strain and subsequently being reluctant to release the isolate to another research group was raised. The existence of reference strain collections was noted. It was recommended that a reference laboratory should be established to build up such a collection from current and prospective future work in developing countries.

International collaboration. The working group should continue its international collaboration in promoting research and control of tuberculosis with special interest in zoonotic aspects. Particular support should be given to the improvement of diagnostic techniques including bacteriology, isolation, typing of mycobacteria, standardization of PPD, enzyme immunoassay, γ -interferon blood test, PCR, and other research at molecular levels.

The group should provide information, with any required technical support, on bovine tuberculosis in key areas such as epidemiology, diagnosis, prevention and control, as well as any requested research

information. In this context, scientists working in bovine tuberculosis, particularly in Africa, should be encouraged to participate in the working group's activities.

WHO through its VPH unit and tuberculosis programme, will continue to be a focal point for international cooperation to promote the above recommendations and to provide support for research groups.

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