

Commentary

Natural reservoir, zoonotic tuberculosis & interface with human tuberculosis: An unsolved question

Mycobacterium bovis is an important member of the *M. tuberculosis* complex. Although it is primarily recognized as an animal pathogen it can cause disease in humans too. Similarly, *M. tuberculosis*, though a human pathogen does infect animals.

It is believed that as the human civilization has advanced through various stages of evolution it has acquired many diseases along side with the fruits of progress. For instance, it has been suggested that many diseases could not have existed in humans prior to the development of agriculture¹. The hypothesis is that farming led to enhanced availability of food which in turn increased population size favourable for maintenance of infectious pathogens in the population. Such pathogens though virulent possibly could not have persisted in small, pre-agricultural population. This argument led to the traditional view of the connection between farming, disease and humans that the pathogens were derived from domestic animals. Me Neill wrote, "Most and probably all of the distinctive infectious diseases of civilization transferred to human populations from animal herds. Contacts were closest with the domesticated species, so it is not surprising to find that many of our common infectious diseases have recognizable affinities with one or another disease afflicting domesticated animals"². Many of the fatal civilizational diseases such as measles, tuberculosis, small pox, influenza, pertussis and falciparum malaria, are believed to have arisen this way³.

M. bovis is an ancient pathogen that causes disease in humans and remains enzootic in wild as well as domestic animals. It is believed that human pathogen *M. tuberculosis* is evolved from *M. bovis* and then developed into a phylogenetically distant species⁴. In recent report Taylor *et al*⁵ analysed ancient DNA (aDNA) from spinal lesion samples collected from iron age humans. Osteological samples were obtained from five individuals with skeletal

evidence of tuberculosis (TB) from cemetery of Aymyrlyg, in the Vlag-Khemski region of Tuva, South Siberia. By applying molecular techniques they were able to detect *M. bovis* infection in 4 out of 5 specimens examined. Phylogenetic analysis revealed loss of DNA from RD4, region of the genome, which defines that classic *M. bovis* had already occurred from the genome of mycobacteria over 2000 years before the present⁵.

Among the wild animals, monkeys, deer and elephants suffer from tuberculosis and probably maintain the sylvatic cycle of tuberculosis whereas domestic animals, mainly cattle maintain the infection in the agricultural and farm lands. Although the wild animals and cattle commonly do not come in contact with each other, transmission of *M. bovis* from domestic animals to wild life (spillover) and subsequent spillback continued over the millennia. It is a cycle that kept the disease going among animals and also in those human populations that came in close contact with *M. bovis* infected animals due to reasons such as agriculture, animal husbandry or hunting related activities⁶. The epidemiology of *M. bovis* in countries like UK has revealed that certain small animals such as the badgers played a major role in maintaining *M. bovis* infection in cattle herds in the farm lands. As a result, those humans who came in close contact with the infected cattle such as animal handlers, hunters and veterinarians frequently suffered from *M. bovis* infection⁷. With effective measures to control the badger colonies in the agricultural lands *M. bovis* infection became sporadic in those areas. In the more recent past *M. bovis* infection occurred in those who consumed unpasteurized milk or insufficiently cooked bovine meat. With the practice of pasteurization of milk and discontinuation of use of raw milk to prepare cheese, *etc.*, the incidence of *M. bovis* infection reduced drastically⁶. At present it is sporadic in the areas where pasteurization of milk is

practiced routinely. Incidentally the continued practice of making a certain kind of popular cheese from raw milk in Mexico and its consumption in the immigrants in US is a major concern to control *M. bovis* infection in that community⁸. In some parts of Africa, where milk is consumed raw, *M. bovis* infection is still endemic⁹.

In contrast, tuberculosis caused by *M. tuberculosis* is still a global problem that is yet to come under effective control in many parts of the world. It is generally believed that although animals contract and suffer from *M. tuberculosis* infection, humans are the natural reservoirs of tuberculosis. Therefore, the focus of TB control programmes in the endemic countries has been BCG vaccination and anti-tuberculosis therapy to the tuberculosis patients. The question of possible transmissions of *M. tuberculosis* between domestic animals and humans have largely remained an academic exercise. In that context the article by Srivastava *et al*¹⁰ appearing in this issue brings out a very interesting and important point. The authors investigated the rate of isolation of *M. bovis* and *M. tuberculosis* from various specimens collected from cattle suspected to be suffering from tuberculosis. The cattle were from organized cattle farms of north India. The results of their investigation revealed that 28.5 per cent of the milk samples collected were culture positive for *M. tuberculosis*. Moreover, 7.1 per cent of pharyngeal swabs taken from animals were also positive for *M. tuberculosis*. The authors propose that it may be possible that the animal handlers are infected by tubercle bacilli and by indiscriminate spitting and urinating in the grazing area of the cattle contaminate the same and animals ingest the bacilli along with their feed and suffer from TB.

This finding opens up a new area for consideration under tuberculosis control programme. In case such a cycle continues in the farming community the operational aspects and the mode of cutting off the transmission of tuberculosis within such a defined community or area will need a fresh thinking.

The results of *M. bovis* isolation are equally alarming. About 19 per cent of tuberculin negative apparently healthy cattle were culture positive for *M. bovis*. 15 per cent of milk samples were also positive for *M. bovis*. This raises a strong possibility of occurrence of bovine tuberculosis infection in humans living in the farms. The epidemiology of bovine tuberculosis in humans in India is insufficiently explored. Like the badgers in UK and other countries where this animal has been shown to maintain infection

as the interface between wild animals and domestic animals, there is no report from India to find out whether any such cycle goes on in the wild animals that frequent the farm lands. It may be useful to initiate investigations to explore the possibility of occurrence of bovine tuberculosis in those wild animals who may act as reservoirs of this disease that probably maintain *M. bovis* infection in the wild animals and spillback to domestic animals. Additionally, although economic loss due to loss of cattle and milk production has been a major concern, the incidence or prevalence of *M. bovis* tuberculosis among humans living and working in close contact with the cattle herds has not been addressed sufficiently in India. No data on rate of infection of humans by *M. bovis* are available.

One of the reasons for unavailability of information on bovine tuberculosis in humans is difficulty to diagnose *M. bovis* infection. Most of the human infections due to *M. bovis* manifest as extra-pulmonary disease, such as gastrointestinal TB. Appropriate and adequate samples are difficult to obtain for laboratory diagnosis of extra-pulmonary TB. Moreover the conventional methods take a long time and not many laboratories are equipped to carry out complex biochemical tests to differentiate *M. bovis* from *M. tuberculosis*. The recent reports on development of rapid molecular methods to differentiate *M. bovis* from *M. tuberculosis* raises a hope for improved detection of bovine and human tuberculosis¹¹. By using PCR diagnostics Shah *et al*¹² showed that among cerebrospinal fluid specimens from TB meningitis patients from India, 17 per cent were positive for *M. bovis* and 2.8 per cent were positive for *M. tuberculosis*¹².

India is endemic for tuberculosis. And, there is an intense effort at the national level by the Government of India to control TB. BCG vaccination at birth and active case finding and implementation of DOTS programme (RNTCP) are making an impact on the Indian TB scenario. However, prevalence of multi drug resistant (MDR)-TB and emergence of extensively drug resistant (XDR)-TB has added a new dimension to the current RNTCP initiatives. In that context the possibility of presence of *M. bovis* tuberculosis with inherent pyrazinamide resistance in certain communities and occurrence of *M. tuberculosis* infection in agricultural and farm land cattle herds as has been reported in this issue by Srivastava *et al*¹⁰ deserve urgent attention.

These questions need to be addressed by systematic investigations. Concerted application of the conventional and precise molecular

epidemiological tools along with clinical, radiological and newer imaging methods in a well designed prospective study may throw some light on the very complex interaction of the environment, host and pathogen in tuberculosis.

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