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Genetic and management factors that influence the susceptibility of cattle to *Mycobacterium bovis* infection

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Abstract

Genetic variation in the susceptibility of cattle to *Mycobacterium bovis* infection exists in differences between families and species, but not breeds. Susceptibility to *M. bovis* infection increases with age of cattle. Natural exposure to *M. bovis* or environmental mycobacteria may assist in the development of specific immunity, but there is no direct evidence for such immunological priming of tuberculosis resistance in cattle. This has, however, been demonstrated in humans and other animals. Since non-specific mechanisms have a role in protective immunity, developing an effective vaccine will be difficult, even though some protection of other species has been achieved. Immunological suppression in the periparturient period can produce anergic reactors, which may act as a constant source of infection for cattle-to-cattle transmission. Circumstantial evidence suggests that an adequate intake of mineral, vitamin and protein reduces the susceptibility of cattle. Although weather patterns have been implicated in the susceptibility of herds to *M. bovis* infection, there is insufficient information to determine the risk factors precisely. It is concluded that some reduction in the susceptibility of cattle to *M. bovis* infection can be achieved by modifications to the management system to minimize risk factors, but that a considerable amount of further research is required.

Historical background

The bacillus *Mycobacterium bovis* was discovered in 1882 by Robert Koch (1843–1910), who first showed that different organisms cause tuberculosis in cattle and man. It has a wide range of both target organs (lungs, gastrointestinal tract, mammary gland, kidney and reproductive organs) and mammalian hosts. Bovine tuberculosis was recognized as a significant problem in cattle production in the early part of the last century (Smith, 1905) and probably existed long before that. In the 1920s, a control strategy was initiated in the UK, which included cattle testing and slaughter of reactor cattle combined with the following management regulations (Fishwick, 1952): (i) 'Double fencing of attested farms to ensure adequate isolation from non-tested cattle'; (ii) 'Movement of attested cattle to shows or sales governed by movement permits issued by local Veterinary Officer of the Ministry of Agriculture'; (iii) 'Only attested cattle introduced directly into attested herds without being isolated (if from non-tested herds they had to be tested after isolation for not less than 60 days)'.

These strategies led to a reduction in prevalence of the disease to less than 0.05% of all herds in England and Wales in the late 1970s. Since that time, the incidence of *M. bovis* infection in England and Wales has increased steadily, so that by 1999 the rate of new infection was 2.4% of the number of unrestricted herds tested (Ministry of Agriculture, Fisheries and Food, 2000). In the current situation, increasing the frequency of testing cattle is not

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likely to influence the prevalence of tuberculosis where there is an extensive wildlife reservoir (Barlow *et al*., 1997). However, in the USA, where there is no wildlife reservoir in regular contact with cattle, the disease has been reduced to a low level, at a cost of US$450 million (Nelson, 1999). There has been an intensive programme of testing, removal and slaughter of infected cattle, begun in the first half of the 20th century (Yapp and Nevens, 1944). Many American cases of *M. bovis* infection are now in imported cattle from Mexico (Essey and Koller, 1994). However, in Michigan State, which has regions where cattle have been infected endemically with *M. bovis* (Towar, 1964), the infection has also been isolated in deer and even coyotes that consume the deer (Schmitt *et al*., 1997; Bruning Fann *et al*., 1998).

There have been several recent reviews of the epidemiology of *M. bovis* infections in animals and man (Morris *et al*., 1994; O'Reilly and Daborn, 1995; Neill *et al*., 2001). There are also reviews of the survival of *M. bovis* in dairy products (Keogh, 1971), its potential transmission to humans (Kovalyov, 1989; Collins, 2000) and transmission in cattle (Griffin and Dolan, 1995), badgers (Cheeseman *et al*., 1989; Gallagher and Clifton-Hadley, 2000) and other wildlife (de Lisle *et al*., 2001). Vaccine development has been reviewed recently by Buddle *et al.* (2000) and Skinner *et al.* (2001).

Genetic variation and selection pressure

Genetic variation in resistance to *M. bovis* infection is manifest at three levels: species, breed and family. In the middle of the twentieth century, when the prevalence of infection was high, the tuberculin testing and slaughter scheme produced significant selection pressure for disease resistance in British cattle. However, in the last three decades the prevalence of the disease has been very low; removal of infected animals has had much less impact on the genotype of the national herd and may have been compounded by the importation of semen from overseas.

Species

Bos indicus cattle are less susceptible than *B. taurus* to *M. bovis* infection (Carmichael, 1941; Ram and Sharma, 1955). If the genes for this effect could be identified within *B. indicus* cattle, they could potentially be transferred genetically to *B. taurus* cattle or used for marker-assisted selection within the *B. indicus* species.

Breed

There is little published information on breed susceptibility, a small study in Latvia having indicating no differences in susceptibility between the major *B. taurus* cattle breeds in Latvia (Petukhov, 1981). Unpublished data from the UK also suggests no differences between British breeds (Benham, 1985). There is, however, some evidence of differences in susceptibility between pure-bred zebu (*B. indicus*) cattle and zebu crosses in Malawi (Ellwood and Waddington, 1972).

Familial genotypic variation

There is evidence that certain familial lines of cattle show particular susceptibility to *M. bovis* infection (Maddock, 1934; Petukhov, 1981). The latter author investigated two cattle farms with 2742 animals in Latvia, where 23% were infected, and noted that some families had 80% of their members infected, whereas others had none. However, it is not clear whether some cattle are completely resistant to the infection. A high rate of transmission from cattle that had been infected artificially with high doses to naive cattle was recorded by Cassidy *et al.* (1999), but in another study only 40% of steers that were initially negative reactors to the single intradermal (SID) comparative tuberculin test developed tuberculosis when housed with reactors for 1 year (Costello *et al*., 1998). Cattle receiving lower doses, for example from contaminated pasture, show low rates of infection (Schellner, 1956), which is supported by the fact that the majority of herd outbreaks involve only a small number of animals.

In experimental animals, strains of tuberculosis-resistant and susceptible mice and rabbits have long been recognized and utilized for research purposes (Wright and Lewis, 1921; Lurie, 1941; Anderson *et al*., 1991). Furthermore, in mice there is a specific single dominant autosomal gene (*Bcg*), the presence of which results in increased macrophage action and interleukin 2 secretion (Schurr *et al*., 1991; Skamene, 1991). In humans, there is both racial and ethnic variation in susceptibility to tuberculosis (Bellamy *et al*., 2000; Lim, 2000), and it has been shown that genetic differences in macrophage protein expression partially determine the resistance shown by humans to *M. tuberculosis* infection (Agranoff *et al*., 1999). In deer, *M. bovis*-resistant stock have been bred by selecting resistant sire lines. The heritability of resistance to tuberculosis has been estimated as 0.48, and both innate and acquired mechanisms of immunity are believed to be involved (Mackintosh *et al*., 2000).

It can be concluded that familial variation in resistance is likely to exist, but at present there is little information on which to base selective breeding. The low and unpredictable level of exposure to infection in the field and the possibility of detecting only those cattle that have mounted a cellular immune response both mitigate against the identification of cattle that are able to eliminate the organism. Experimental identification of resistant cattle would require a significant resource provision, given the need for disease containment facilities for the infected cattle.

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Mechanisms of immunity and possible genetic influence

Established infection with *M. bovis* is still a relatively rare event in the UK. The rate of new infection in 1999 was 2.4% of the number of unrestricted herds tested (Ministry of Agriculture, Fisheries and Food, 2000), and most herd breakdowns involved only very few reactor animals (Wilesmith *et al.*, 1986; Wilesmith and Williams 1986). Natural infection is thought to be frequently derived from the multiplication of a single bacillus (Neill *et al.*, 1991). The exposure rate of cattle in high-risk herds remains unknown. Low-dose exposure may be common, the animals' non-specific immune mechanisms eliminating the mycobacteria before infection becomes established. It has been estimated that an antigenic load of approximately 1000 mycobacterial organisms is required before cell-mediated immunity is activated (Smith and Wiegeshaus, 1989; Dannenburg, 1991). Therefore, animals with a negative skin test may have been exposed to a low-dose challenge of *M. bovis* bacilli and successfully eliminated the organisms by non-specific immune mechanisms before they multiplied. Neill *et al.* (1992) reported a case of transient nasal excretion of *M. bovis* from an in-contact calf which showed no skin test response and no lesions at slaughter. If low-dose exposure to *M. bovis* is widespread in herds with repeated evidence of infection, the efficiency of non-specific immune responses may be critical in determining whether an animal develops infection.

Many mechanisms of non-specific immunity could be effective in eliminating a low-dose *M. bovis* challenge. Those under genetic influence might include the chemical nature of the bronchial mucus, the efficiency of the mucociliary escalator, the number of active non-specific macrophages in the lungs and the destructive efficiency of these macrophages' lysosomal enzymes. Other genetically controlled factors influencing susceptibility to bovine tuberculosis may be behavioural. The animals' grazing habits with respect to the avoidance of excretory products, the amount of social behaviour that might facilitate cattle-to-cattle transmission, and investigation by cattle of badgers or their excreta, may all be genetically influenced.

Specific mechanisms of immunity will almost certainly be genetically influenced. The type of immune response effected in human tuberculosis depends largely on the way mycobacterial antigen is presented by the genetically controlled major histocompatibility complex class II molecule (Orme, 1991). The mycobacterial epitopes presented will determine the classes and proportions of lymphocytes recruited. The predominant classes of lymphocytes recruited will greatly influence whether the disease progresses to the fulminating stage or is effectively limited.

Active immune responses to *M. bovis* infection

Specific active immunity to *M. bovis* through the generation of appropriate classes of sensitized lymphocytes and memory cells may theoretically be generated by three mechanisms: natural exposure to *M. bovis*, exposure to other mycobacteria, and vaccination. The use of a supplementary humoral test may detect the presence of some anergic cows (Plackett *et al.*, 1989; Wood *et al.*, 1990; Hanna *et al.*, 1992; Whipple *et al.*, 1995), in which the cellular immune mechanism is suppressed in both the peripheral blood and at the site of the disease (Lepper *et al.*, 1977; Rhodes *et al.*, 2000). Plackett *et al.* (1989) identified a group of cattle that had high levels of antibody response against *M. bovis* but were negative to the tuberculin test. The interferon-γ released by lymphocytes can prime macrophages to greater microbicidal activity prior to mycobacterial infection, and a blood culture interferon-γ enzyme immunoassay system is a useful adjunct to skin testing for the detection of bovine tuberculosis infection.

Natural exposure to M. bovis

Francis (1947) took the pessimistic view, that unlike in man, in cattle the primary lesions are rarely if ever arrested. However, in natural infection in the field, the prevalence rate rarely exceeds 50% within a group (Waddington and Ellwood, 1972). This suggests that in the field, when disease prevalence is greatest (and cattle-to-cattle exposure to *M. bovis* is almost inevitable) a substantial proportion of animals are able to mount an effective protective response to *M. bovis* exposure. As most of these animals remain negative in the tuberculin test, any effective but non-specific immune response (e.g. through powerful microbicidal macrophages) will remain undetected. If specific cellular immunity is generated by natural exposure to *M. bovis*, such animals will be positive to the tuberculin test (yet reveal no visible lesions or positive culture) at slaughter. Interestingly, Wilesmith and Williams (1987) showed that, for the period 1979–1983, 70% of non-visible lesioned tuberculin test reactors in south-west England were probably caused by exposure to *M. bovis*. Undoubtedly, a proportion of these animals had lesions present at slaughter that remained undetected (Corner *et al.*, 1990). It remains unclear whether some of these animals mounted a successful specific immune response to *M. bovis*.

In New Zealand, an experimental model has been developed in red deer in which an *M. bovis* infection indistinguishable from natural infection is produced by very low-dose tonsillar crypt challenge with *M. bovis* (Mackintosh *et al.*, 1995). Experimentally challenged animals produced a spectrum of immune responses and clinical disease ranging from no disease to severely disseminated tuberculosis (Mackintosh *et al.*, 2000). Plackett *et al.* (1989) identified a group of cattle with high levels of antibody against *M. bovis* but negative to the SID tuberculin test. Harboe *et al.* (1990) and Ritacco

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et al. (1991) were able to demonstrate an inverse relationship between titers of specific *M. bovis* antibody and cellular responses in experimental cattle. Other workers also accept this concept of a spectrum of immunological response to mycobacteria (Lepper and Corner, 1983; Buchan and Griffin, 1990; Buchan *et al.*, 1991; Neill *et al.*, 1994).

Exposure to other mycobacteria

Pre-exposure to environmental mycobacteria may, by mechanisms of immunological cross-reactivity, alter the course by which the disease progresses when an individual is challenged with a mycobacterial pathogen (Stanford *et al.*, 1976; Shield, 1983; Pallen, 1984; Grange, 1986, 1987; Grange and Collins, 1987). Other, naturally occurring mycobacteria grow well in soil (Iivanainen *et al.*, 1999) and saprophytic vegetation, particularly bryophytes (Cooney *et al.*, 1997). Members of the *Mycobacterium avium–intracellulare–scrofulaceum* complex predominate in water, dust and human sputum samples and *M. fortuitum* links with organisms in the soil (Kamala *et al.*, 1994). Environmental mycobacteria are also ubiquitous in natural water supplies (Dailloux *et al.*, 1999), where they inhabit the surface biofilm (Hall-Stoodley and LappinScott, 1998).

Most environmental mycobacteria are capable of inducing non-specific reactions to bovine and avian tuberculin (Cooney *et al.*, 1997; Corner and Pearson, 1979), which may influence the susceptibility of cattle to *M. bovis* infection. Guinea-pigs that have been immunized with *M. fortuitum* show a modulated protective response with the BCG vaccine (Kamala *et al.*, 1996). There is no direct evidence for this in cattle, but the immunological priming of humans and other animals by exposure to environmental mycobacteria is well established (Donoghue *et al.*, 1997). A study in south-west England found that a change in the distribution of predominating mycobacteria coincided with the introduction of organic farming practices, which, it is suggested, could increase the potential immunity afforded by exposure to non-pathogenic types (Donoghue *et al.*, 1997). However, although there is circumstantial evidence, there is no definitive research that suggests that alterations in susceptibility are possible as a result of prior or concurrent exposure to mycobacteria of different species or to other, less closely related organisms (Morris *et al.*, 1994).

The possibility that the consumption of environmental mycobacteria enhances the immune response to *M. bovis* cannot be dismissed, but it is unclear why such immunological priming was not effective in the early part of the last century, when *M. bovis* infection was even more common than it is today. It is possible that any effect was not sufficient to overcome major challenges from other highly infectious cattle at that time. Many cattle in those days were poorly nourished in winter and were kept in under-ventilated and densely stocked buildings.

Vaccination

Other pathogenic mycobacteria affecting cattle, such as *M. avium* ssp. *paratuberculosis*, cannot be entirely controlled by vaccination, even after 100 years of research (Johnson-Ifearulundu and Kaneene, 1997). In New Zealand, some protection of possums from *M. bovis* infection has been possible by injecting them with the BCG vaccine (Aldwell *et al.*, 1995). However, assuming that an extensive wildlife reservoir exists in the UK, any cattle vaccine would have to have an efficacy of more than 97% (Kao *et al.*, 1997).

The development of a cattle vaccine against *M. bovis* infection is at present a priority research objective in the control of bovine tuberculosis. An effective vaccine would prove a most practical and useful husbandry tool in the control of *M. bovis* infection in cattle. However, any live tuberculosis vaccine is unlikely to confer complete protection within a population and should be seen as a tool for disease control, not eradication. Since non-specific mechanisms have an important role in protective immunity, vaccination is likely to have less effect compared with improving nutrition or selecting for disease resistance.

Recent studies using a BCG and red deer model in New Zealand have been more encouraging, low-dose vaccination being able to protect a proportion of vaccinates against infection and lessen the severity of disease in others (Mackintosh *et al.*, 2000). However, Mackintosh *et al.* suggest that genetically susceptible deer may be incapable of developing a protective immune response to the *M. bovis* BCG vaccine.

Type of cattle enterprise

Cattle farming systems have increased the intensity of production in recent decades, as evidenced by increases in the milk yield and growth rate of cattle. However, in non-refereed Irish reports of the risk of herd breakdown by enterprise type (dairy, suckler and drystock units), no differences in breakdown rate were observed (Fallon, 1994; Mairtin, 1994). A smaller study in Italy showed that mixed dairy and beef enterprises were at greater risk of breakdown than either dairy or beef herds, which may have been due to increased likelihood of cattle movement, a major risk factor (Marangon *et al.*, 1998). Herd size does not influence the chance of a breakdown in the herd (Marangon *et al.*, 1998); thus the risk per animal is greater in small herds. This may be because the field boundaries are less contiguous in large herds.

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In conclusion, there appears to be little evidence yet that changes in the type of cattle enterprise following a breakdown would be beneficial, but large herds have a reduced risk per animal.

Age

An increase in disease prevalence with the age of cows has been recorded both in Latvia, where the mean age of onset was 6 years (Petukhov, 1981), and in the UK, where the relative risk to cows over 8 years of age was 12 times the risk to cows aged 1–2 years (Benham, 1985). In Mexico, where there is a significant proportion of infected cattle, most reactors are adult females in fair to good body condition (Milian-Suazo *et al*., 2000). Francis (1947) writes 'the evidence suggests that even when young cattle are pastured with heavily infected old stock, the incidence in the former remains low until they enter the cow shed.'

Physiological state

Pregnancy has been implicated in anergy to the tuberculin test. There is a suppression of skin reactivity for about 15 days around parturition (5 days before to 10 days after calving) (Kerr, 1949). A similar reduction in skin reactivity after calving was observed by Buddle *et al.* (1994), together with a temporary reduction of the response in the interferon-γ immunoassay. This could be associated with the periparturient immunosuppression in dairy cows, which derives partly from nutrient deficiencies (Kehrli, 1998). There is no effect of pregnancy on disease susceptibility (Buddle *et al*., 1994).

Exogenous corticosteroids

Corticosteroids are well known for their immunosuppressive effects, and corticosteroid production by the calf at parturition may be associated with the periparturient immunosuppression referred to above. Kerr *et al.* (1949) report suppressive effects of corticosteroids on the tuberculin test. Corticosteroids are used in medicine to prevent the rejection of foreign tissue grafts and in the treatment of allergic disease, and they may be used therapeutically (e.g. for the induction of parturition or the treatment of ketosis). Their use may increase an animal's susceptibility to infection. With the recent availability of licensed non-steroidal anti-inflammatory drugs for cattle, corticosteroids are now used much less commonly in general practice. Corticosteroids could theoretically be used by unscrupulous cattle owners to conceal tuberculous animals, but this might not be effective and would be counterproductive.

Concurrent diseases

Immunosuppressive disease

The effect of concurrent immunosuppressive disease on *M. bovis* infection in cattle does not appear to have been investigated. However, the major influence of HIV infection in humans on the risk of subsequent infection with *M. tuberculosis* or other mycobacteria is well documented (e.g. Glynn *et al*., 2000; Mukadi *et al*., 2001). A severe outbreak of *M. bovis* infection in housed calves with concurrent bovine viral diarrhoea (BVD) infection has been reported (Monies and Head, 1999). BVD is capable of producing immunosuppression (Potgieter *et al*., 1984). Concurrent infection with feline immunodeficiency virus (FIV) and *M. bovis* in farm cats has been reported (Monies *et al*., 2000). It is to be expected that immunosuppressive diseases will increase susceptibility to infection: examples are BVD, enzootic bovine leukosis and bovine immunodeficiency-like virus, even though the latter may not produce an immunodeficiency syndrome like HIV or FIV, and hemolytic diseases such as babesiosis and tick-borne fever.

Diseases that are not intrinsically immunosuppressive may also affect susceptibility to *M. bovis* infection, such as those affecting vascular permeability or serum protein levels, which may indirectly affect cell-mediated immune responses (e.g. protein-losing enteropathies/nephropathies, fascioliasis, haemonchosis and ostertagiasis).

Respiratory disease

Dictyocaulus viviparus (Husk), *Pasteurella* spp., *Mycoplasma* spp., *Haemophilus* spp., infectious bovine rhinotracheitis virus, BVD, parainfluenza type 3 virus and Rous sarcoma virus are all pathogens responsible for causing respiratory disease in cattle. Their influence on susceptibility to infection with *M. bovis* remains unclear. Clinical effects associated with these diseases include pneumonia, bronchitis, tracheitis and altered bronchial mucus and secretions. Not only is it likely that they make the respiratory membrane more susceptible to infection with *M. bovis*, but those agents which induce coughing may also facilitate increased dissemination of *M. bovis* in aerosol form.

Nutrition

Low food intake did not increase the risk of transmitting *M. bovis* infection between steers in a study by Costello *et al.* (1998), but replication of the experimental unit was low. In a study in Mexico, cattle that were infected with *M. bovis* were reported to be mostly in fair to good

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body condition (Milian-Suazo *et al*., 2000). However, since protein deficiency has been shown to reduce immunocompetence in guinea-pigs (McMurray *et al*., 1989), it is possible that there are nutritional effects in cattle that have not been elucidated. Experience from collective farms in Czechoslovakia suggests that deficiencies in vitamins A and C, calcium and protein, as well as carbohydrate excess, are likely to increase the risk of cattle acquiring *M. bovis* infection (Kabrt, 1962).

Mineral supplements

There is epidemiological evidence of an association between the provision of mineral licks and *M. bovis* infection. An Irish study found that the provision of mineral licks reduced the risk of a herd acquiring *M. bovis* infection in a study of breakdown herds, with an odds ratio of 2.7 (Griffin *et al*., 1992, 1993). As in early 20th-century experience (Garner, 1946), the risk was also greater on farms with rough grazing, which may have been due to protection from sunlight or inadequate nutrition of the cattle. In the study by Griffin *et al.* (1992, 1993), the risk of breakdown was much greater on farms where there was a combination of no mineral lick being available and rough grazing. The effect of rough grazing was attributed to inadequate mineral supply from low-quality pasture. This led to the conclusion that mineral deficiencies predispose cattle to the disease. However, later (non-refereed) reports from Ireland found no relationship between three of the minerals likely to be deficient in cattle (copper, selenium and iodine) and the prevalence of *M. bovis* infection (Fallon and Rogers, 1993). However, it is possible that the provision of other minerals commonly provided in mineral licks (sodium, magnesium, zinc and cobalt) was responsible for the observed benefits in the work of Griffin *et al.* (1992). Published requirements for sodium for dairy cows are now believed to be too low, and there is evidence that increased sodium intake can reduce other diseases in dairy cows (Phillips *et al*., 2000). This may be due to enhanced magnesium absorption, as the inhibition of magnesium absorption in the rumen by potassium is negated by the presence of sodium (Chiy and Phillips, 1993). In laboratory animals at least, magnesium status is an important factor in the immune response, magnesium deficiency leading to reduced antibody concentrations and activity (McCoy and Kenny, 1992). Magnesium is commonly deficient in grazing cattle, and in another pathogenic mycobacterial disease, leprosy, the magnesium status of the host is reduced (Jain *et al*., 1995).

There is evidence that specific mineral deficiencies play an important role in predisposing animals to other mycobacterial infections. The low iron status of rodents increases their susceptibility to paratuberculosis; however, in cattle high susceptibility to copper deficiency may also mean that a high iron intake could predispose cattle to the disease, since iron competes with copper for absorption sites (Lepper *et al*., 1989). Copper and zinc superoxide dismutases protect against exogenous superoxide radicals and thereby may determine the virulence of pathogenic mycobacteria (Wu *et al*., 1998). Alternatively, cadmium is a well-known antagonist of zinc and there is some evidence that badgers, a major intermediate host in Eire, are susceptible to the increased levels of cadmium in pasture in recent years, which reduces their reproductive rate and could impair kidney function (Vandenbrink and Ma, 1998). The possibility that in the Irish research the mineral licks at pasture improved the health of badgers rather than cattle cannot be ruled out. The licks usually contain zinc, which could offset high cadmium intakes.

The sporadic distribution of mycobacteria in the environment is partly due to their high susceptibility to the supply of minerals, particularly iron. Most mycobacteria are tolerant of acid soil conditions but are inhibited by the reduced iron availability in alkaline soils (Mitserlich and Marth, 1984). Mycobacteria are not good at chelating iron and they secrete siderophores to sequester the element externally (Johnson-Ifearulundu and Kaneene, 1997). In a review of the effects of soil type on the prevalence of paratuberculosis in cattle, Johnson-Ifearulundu and Kaneene (1997) noted many studies reporting that the disease is more prevalent in areas with acidic soils, in which there is increased availability of minerals. The prevalence of other diseases, most notably anthrax, which is caused by *Bacillus anthracis*, and fusarium wilt, which is caused by *Fusarium oxysporum*, has been demonstrated to vary directly with soil pH (Johnson-Ifearulundu and Kaneene, 1997). This is due, at least in the case of fusarium wilt, to the restriction of iron availability at high pH. An association between the prevalence of paratuberculosis in cattle and soil pH, while not proven empirically, is supported by evidence from the geographical distribution of the disease and the significant requirements of *M. paratuberculosis* for iron (Johnson-Ifearulundu and Kaneene, 1997). No such association has yet been demonstrated for *M. bovis* infection of cattle, but outbreaks occur regularly in regions with calcareous soils.

Another pathogenic mycobacterium, *M. leprae*, reduces the systemic status of zinc and iron in its hosts (Jain *et al*., 1995). In *M. bovis* infection, siderotic macrophages containing mycobacteria are seen in early granulomas, but in later stages epithelioid and giant cell differentiation reduces the intracellular concentration of iron and the number of mycobacteria (Lepper and Wilks, 1988). Whilst it might be suspected that this is due to localized effects in the affected region, and in particular the high zinc content of the bacteria, the same changes in mineral status have been observed in humans with pulmonary tuberculosis (Narang *et al*., 1995). Changes in the levels of biometals in the sera of leprosy patients may be due to a systemic effect, in par-

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ticular the release of interleukin 1. This product of inflammatory cells causes hypercupremic, hypozincemic and hypoferremic responses in the hosts (Jain *et al*., 1995), which may reduce mycobacterial proliferation. Again, no such relationship has been demonstrated for *M. bovis* infection, and preliminary (non-refereed) evidence is that the copper status of cattle is not involved in herd breakdowns (Fallon and Rogers, 1993). However, further investigations of the micronutrient status of breakdown herds would appear worthwhile.

In summary, there is evidence that other pathogenic mycobacterial diseases alter the mineral status of animals, but it is unlikely that the micronutrients most commonly believed to be deficient in cattle are associated with the risk of *M. bovis* infection. It seems unlikely that the elements which protect the host from oxidative damage, such as copper and selenium, can explain differences in susceptibility. Some other minerals commonly believed to be in deficit could explain why the presence of mineral licks reduces the risk of *M. bovis* infection.

Weather

It is likely that the transmission of *M. bovis* is affected by weather conditions, since it can be destroyed by ultraviolet light in sunlight (Soparker, 1917). King *et al.* (1999) found that the annual prevalence of *M. bovis* increased in direct proportion to rainfall in the previous year, but this association is based on only a single study area. They also examined seasonal weather effects, but the large number of possible associations tested meant that those demonstrated could be spurious. Climate may help to explain the geographical localization of *M. bovis* infection in the south-west region of the UK. According to King *et al.* (1999), the link with climate also suggests that infection is more likely to be field-based than to act through infection indoors. If cattle were infected in early summer, disease could spread to others during confinement the following winter, leading to high numbers of infected animals being detected early in the following year. However, testing in the region studied by King *et al.* is more intensive in spring, obscuring seasonal patterns, and annual testing is insufficiently frequent to determine patterns of infection within years. As well as affecting cattle management and *M. bovis* survival, climatic factors may also affect the behaviour of cattle (Phillips, 1993) and badgers, which could influence the likelihood of transmission.

Housing

Despite the assertion by King *et al.* (1999) that transmission of infection is more likely at pasture, the authors of books on cattle in the first half of the last century, when bovine tuberculosis was endemic, did not doubt that transmission between cattle was much more likely indoors than at pasture (Smith, 1905; Garner, 1946; Francis, 1947). However, at that time the disease would normally have progressed to a more infectious state than today, when there is regular tuberculin testing. It is also recognized that housing type and quality are significant risk factors for human tuberculosis and for paratuberculosis in cattle (Collins *et al.*, 1994; LoBue *et al.*, 1999).

Conclusions

There is evidence for genetic variation between cattle in resistance to *M. bovis*, but it is not clear either how complete the resistance is in the face of a major challenge or whether the variation is greatest between different species, breeds or families. Research to determine whether there are genetic differences in the specific and non-specific responses to infection could ultimately enable resistant cattle to be bred. Immunological priming may also influence the scale of the responses, but there is no direct evidence of this yet in the responses to *M. bovis* infection in cattle. Vaccination may eventually provide a means of control, not eradication, and has proved to be effective in deer. The major risk factors associated with management that have been linked to *M. bovis* transmission include small herds, mixed beef and dairy herds, older cows, probably undernutrition, particularly of minerals, and inadequate ventilation of cattle buildings. There is probably also an increased risk to cows around parturition. A considerable amount of further research is required on most of these factors before farmers can substantially reduce the risk of *M. bovis* transmission by modifications of their husbandry techniques. (For a summary of husbandry practices that could influence the disease prevalence, see Appendix.)

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Appendix

Potential husbandry practices to reduce M. bovis *infection*

This review suggests that a range of factors may predispose cattle to *M. bovis* infection. Although there is no clear evidence of the relative importances of these factors, the following husbandry advice may be recommended on the strength of current knowledge.

- The pursuit of a breeding programme to identify resistant sires may be beneficial, but changes in cattle breed are unlikely to offer any improved resistance. Changes in the type of cattle enterprise are unlikely to reduce the risk *of M. bovis* infection, but larger herds will have a reduced risk per animal.
- Farmers should be aware that old cows are particularly susceptible to infection by *M. bovis* and in some cases may be able to adopt strategies to reduce risk in these cows. For example, they could be kept away from high-risk areas of the farm.
- The provision of mineral licks is associated with a reduced risk of cattle acquiring *M. bovis* infection, but supplementary copper, selenium or iodine is unlikely to affect the risk. The potential exists for badgers visiting mineral licks to transmit the disease via their sputum, but this could be avoided by raising mineral blocks out of the reach of badgers and other relevant wildlife.
- Concurrent disease, particularly of the respiratory tract, and possibly BVD, may increase the susceptibility of cattle. Effective treatment or vaccination is likely to reduce susceptibility to *M. bovis* infection.

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