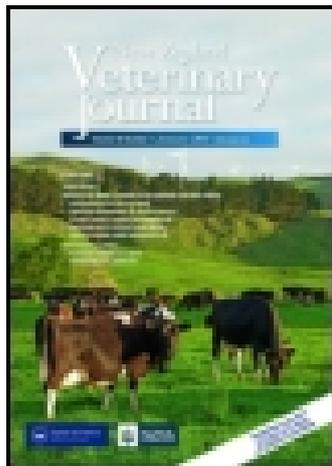


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New Zealand Veterinary Journal

Publication details, including instructions for authors and subscription information:
<http://www.tandfonline.com/loi/tnzv20>

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Accepted author version posted online: 29 Sep 2014. Published online: 12 Mar 2015.

To cite this article: DP Anderson, DSL Ramsey, GW de Lisle, M Bosson, ML Cross & G Nugent (2015): Development of integrated surveillance systems for the management of tuberculosis in New Zealand wildlife, New Zealand Veterinary Journal, DOI: [10.1080/00480169.2014.963830](https://doi.org/10.1080/00480169.2014.963830)

To link to this article: <http://dx.doi.org/10.1080/00480169.2014.963830>

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Review Article

Development of integrated surveillance systems for the management of tuberculosis in New Zealand wildlife

DP Anderson*[§], DSL Ramsey[†], GW de Lisle[‡], M Bosson[#], ML Cross* and G Nugent*

Abstract

Disease surveillance for the management of bovine tuberculosis (TB) in New Zealand has focussed, to a large extent, on the development of tools specific for monitoring *Mycobacterium bovis* infection in wildlife. Diagnostic techniques have been modified progressively over 30 years of surveillance of TB in wildlife, from initial characterisation of gross TB lesions in a variety of wildlife, through development of sensitive culture techniques to identify viable mycobacteria, to molecular identification of individual *M. bovis* strains. Of key importance in disease surveillance has been the elucidation of the roles that different wildlife species play in the transmission of infection, specifically defining brushtail possums (*Trichosurus vulpecula*) as true maintenance hosts compared to those that are predominantly spillover hosts, but which may serve as useful sentinel species to indicate TB persistence. Epidemiological modelling has played a major role in TB surveillance, initially providing the theoretical support for large-scale possum population control and setting targets at which control effort should be deployed to ensure disease eradication. As TB prevalence in livestock and wildlife declined throughout the 2000s, more varied field tools were developed to gather surveillance data from the diminishing possum populations, and to provide information on changing TB prevalence. Accordingly, ever more precise (but disparate) surveillance information began to be integrated into multi-faceted decision-assist models to support TB management decisions, particularly to provide informed parameters at which control effort could be halted, culminating in the Proof of Freedom modelling framework that now allows an area to be declared TB-free within chosen confidence limits. As New Zealand moves from large-scale TB control to regional

eradication of disease in the coming years, further integrative models will need to be developed to support management decisions, based on combined field data of possum and TB prevalence, sentinel information, risk assessment in relation to financial benefits, and changing political and environmental needs.

KEY WORDS: *Wildlife, tuberculosis, Mycobacterium bovis, brushtail possum, surveillance, models, integrated framework*

Introduction

The objectives and techniques used in wildlife surveillance for *Mycobacterium bovis* in New Zealand have evolved from first identifying wildlife hosts of *M. bovis* (Ekdahl *et al.* 1970) to the present-day emphasis on demonstrating freedom from tuberculosis (TB) in wildlife populations (Anderson *et al.* 2013; Nugent *et al.* 2015a). This evolution has been driven by the collaborative feedback loop between management-driven questions and scientific inquiry, resulting in the advances in disease surveillance that have made *M. bovis* eradication from wildlife an achievable and verifiable goal. Management and scientific progress has been made at multiple biological levels: molecular; cellular; whole organism; population; and inter-specific dynamics. In this paper we review and discuss how basic disease management questions led to specific research endeavours, and how this has led to the current stage of integrated surveillance systems for TB in New Zealand wildlife.

Progressive development of diagnostic methods for TB in wildlife

Since the earliest discovery of TB in introduced wild mammals in New Zealand (reviewed in detail in Livingstone *et al.* 2015; Nugent *et al.* 2015a), numerous cross-sectional necropsy surveys of a range of wildlife species have been undertaken by TB management agencies and researchers, to identify TB presence and/or to assess local disease prevalence. Such surveys have involved random or systematic sampling of animals that could be killed and their carcasses recovered for detailed post-mortem

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<http://dx.doi.org/10.1080/00480169.2014.963830>

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REA	Restriction endonuclease analysis
RTCI	Residual trap catch index
SPM	Spatial possum model
TB	Tuberculosis
VRA	Vector risk area

examination (necropsy), or (in the case of pigs and deer) have taken advantage of animals killed by hunters. Over the years species-specific protocols have been developed for efficient necropsy, with those for the main host (brushtail possums, *Trichosurus vulpecula*) formalised into standard operating procedures by TBfree New Zealand.

In early surveys conducted in TB endemic areas, disease was identified in wildlife primarily by the presence of gross lesions suggestive of TB, usually at low to moderate prevalence among possums (Coleman 1988; Jackson *et al.* 1995a,b) but often at much higher prevalence in wild ferrets (*Mustela furo*; Ragg *et al.* 1995a; Lugton *et al.* 1997a), pigs (*Sus scrofa*; de Lisle 1994) and red deer (*Cervus elaphus*; Lugton *et al.* 1997b, 1998; Nugent 2005). Lesions suggestive of TB were also identified at low prevalence in stoats (*Mustela erminea*), cats and hedgehogs (*Erinaceus europaeus*) (Lugton *et al.* 1995; Ragg *et al.* 1995b; Coleman and Cooke 2001). While early surveys of TB in wildlife relied on diagnoses based on the discovery of macroscopic lesions identified during necropsy examinations, histopathology also provided a useful adjunct technique for confirming the presence of mycobacterial lesions as well as eliminating some lesions as not tuberculous (Cooke 2000). A major limitation of histopathology is that it cannot distinguish lesions caused by *M. bovis* from those caused by other mycobacterial species. While macroscopic lesions caused by mycobacterial species other than *M. bovis* are rare they could result in areas being incorrectly classified as having *M. bovis*-infected wildlife. For example, fallow deer (*Dama dama*) infected with *Mycobacterium kansasii* have been recorded in New Zealand, with macroscopic and microscopic lesions indistinguishable from those caused by *M. bovis* (GW de Lisle, unpublished data). Accordingly, mycobacterial culture has been adopted as the gold standard for a confirmative diagnosis of TB due to *M. bovis*, although for cost reasons it was initially used in surveys only to confirm *M. bovis* infection in TB-like lesions detected during necropsy.

One limitation of surveillance based on macroscopic necropsies for TB is the occurrence of *M. bovis*-infected wildlife (including ferrets, possums, pigs and deer) that do not have identifiable lesions. The “no visible lesion” status requires a means of identifying these cases (Gavier-Widen *et al.* 2009). Consequently, in modern surveillance, it is often standard practice to culture material for viable *M. bovis* bacilli from a defined set of tissues from each animal, regardless of whether typical or suspect pathologies are present. Culture has proved a more sensitive method for detecting *M. bovis* in wildlife (de Lisle *et al.* 2005a), compared with gross pathology and histopathology, as a proportion of infected wildlife (particularly possums and ferrets) show no visible macroscopic lesions at necropsy (de Lisle *et al.* 2005a). The selection of samples for culture is determined by the anatomical pattern of distribution of lesions (predilection sites) which differ between hosts. For carnivores or omnivores, such as ferrets and pigs, the most common sites of infection are lymphoid tissues associated with the gastrointestinal tract and head region (submandibular, parotid, retropharyngeal and/or mesenteric lymph nodes) (Lugton 1997; Lugton *et al.* 1997a). In contrast, the majority of macroscopic lesions in possums are found in the superficial lymph nodes and lungs, and in the case of advanced disease, the reticuloendothelial organs; spleen and liver (Coleman 1988; Jackson *et al.* 1995a,b). Wild deer have gross lesions predominantly in the lymph nodes of the head (sub-mandibular and retropharyngeal nodes) and the lungs (Lugton *et al.* 1998; Nugent 2005).

While culture is the most definitive diagnostic for *M. bovis*, it has the disadvantage of taking weeks to months to obtain a result. In addition, successful culture of *M. bovis* relies on good quality samples from which viable mycobacteria can be isolated, which can be difficult to achieve as wildlife are sometimes necropsied under suboptimal conditions. Alternatively, PCR-based tests for *M. bovis* have the advantage of speed when compared to culture (1–2 days *vs.* 4–12 weeks for a result) and they can potentially detect non-viable organisms (Nugent *et al.* 2012). PCR-based tests have been described for *M. bovis* diagnostic use in livestock (Taylor *et al.* 2007; Thacker *et al.* 2011) but less frequently for wildlife species. The detection of *M. bovis* by PCR produces more rapid results than mycobacterial culture but often has the disadvantage of reduced sensitivity. This is especially true when examining necropsy samples containing few bacteria, such as tissues without macroscopic lesions. The high costs associated with wildlife surveys means a common diagnostic approach to reduce analysis costs is to combine pools of predilection-site tissues from 10–30 animals (de Lisle *et al.* 2005a; 2009). In New Zealand this approach is used where the aim is demonstration of presence/absence of *M. bovis* infection at a population level, rather than determining prevalence. Pooling of tissues has the potential to reduce the sensitivity of detecting *M. bovis* in wildlife populations. In one of the few cases of direct comparison of PCR *vs.* culture of wildlife samples (for pooled ferret lymph node tissues samples), culture proved the more sensitive of these two laboratory-based diagnostics (de Lisle *et al.* 2005b).

In 2012 the routine method for DNA typing *M. bovis* in New Zealand was changed from that based on restriction endonuclease analysis (REA) to a PCR-based procedure, which examines variable number tandem repeats and direct repeats of DNA fragments to distinguish between different or related strains of *M. bovis* (Price-Carter *et al.* 2011). While the variable number tandem repeats-based system is slightly less discriminatory than REA, it is faster and simpler to operate. The revolution in DNA sequencing opens the possibility in the near future of using whole genome sequencing as an economical and practical method for typing *M. bovis*.

Application of diagnostic methods to surveillance for TB in possums

The purpose for which survey data for TB in wildlife have been collected and utilised has changed as the TB management directions in New Zealand have changed. Initially, information derived from necropsy surveys was used for defining the areas that contained wildlife infected with *M. bovis*, which was necessary to initiate a co-ordinated nationwide TB management programme and to integrate this information with concurrent TB diagnostic surveillance data from livestock. In addition, information on the distribution of TB in wildlife was used as a guide to target wildlife control operations, especially to prevent the spread of new infection into disease-free wildlife populations, leading to the broad classification of geographical regions as vector-free or vector-risk areas. As further surveys were carried out, these areas were better defined and used to generate spatial maps of TB persistence in wildlife (Livingstone *et al.* 2015).

In the initial stages of co-ordinated surveys of TB in wildlife (the late 1980s until mid 1990s) it was sometimes difficult to

determine whether apparent increases in the area of wildlife with TB were due to actual increases in disease prevalence, or just an ability to better define already existing areas of wildlife with TB, due to more intensive surveying and/or more precise diagnostics. Some of the most important insights into the origins of a particular TB outbreak, and the epidemiological links between wildlife species and livestock, were consequently provided by an ability to distinguish between different strains of *M. bovis* via molecular analyses. Early typing studies using REA showed that possums from different geographical areas were infected with different DNA types (Collins *et al.* 1986), an important indication that there were multiple foci of TB in wildlife of independent origin throughout the country, rather than patchy but contiguous distributions of just one or two common bacterial strains. Subsequently, it was shown that within any given locality, cattle and possums were usually infected with *M. bovis* strains of the same REA type (Collins *et al.* 1988). More extensive typing studies including cattle and farmed deer, possums, ferrets and feral cats, provided insights into the transmission of *M. bovis* among multiple hosts (de Lisle *et al.* 1995). The finding of the same REA type in a wide range of different hosts from the same area supports the concept of maintenance, spillover and dead-end hosts contributing to a multi-species complex of *M. bovis* transmission (Morris and Pfeiffer 1995; Nugent *et al.* 2015a, b). Over 3,500 different isolates of *M. bovis* have been analysed by REA and differentiated into over 300 different types. The host distribution of the most common REA types is summarised in Table 1, indicating the host species complexity of TB in wildlife in New Zealand. Each of these types has been found in both domestic animals and wildlife. To date, no evidence has been found of host-adapted strains of *M. bovis*.

More recently, the aim of wildlife surveys in New Zealand has concentrated on providing evidence of absence of infection following repeated cycles of wildlife control operations (described

below). A major use of molecular strain typing here has been investigation of the origin of new outbreaks of *M. bovis* infection in cattle and farmed deer herds. Typing can show whether or not the strains in cattle and farmed deer are the same as those from local or nearby wildlife: if the strains are different it provides evidence that the infection was likely introduced by stock movement, however if the strains are the same as those in neighbouring wildlife, it provides evidence suggesting spread from that source. Furthermore, it may indicate an extension of the area containing infected wildlife. The finding of clusters of cases of TB in cattle herds suggests a common source of infection and may be indicative of a new focus of wildlife infection.

Methods for estimating possum populations following population control

Efforts at TB mitigation from the early 1990s onwards focussed increasingly on large-scale sustained intensive lethal control of possums to reduce local populations to levels at which *M. bovis* infection could not be maintained (Nugent *et al.* 2015a). By the mid-2000s the herd reactor rates among farmed cattle and deer had been reduced dramatically (Livingstone *et al.* 2015), and surveillance objectives shifted to identifying the absence of *M. bovis* infection among sympatric wildlife as a result of possum control. However, assessment of the reduction in TB prevalence in possums was difficult because the low density of possums in managed areas made it difficult to obtain the large sample sizes needed to measure prevalence of *M. bovis* infection with high statistical precision. The use of pooled samples of predilection site tissues (described above) from ferrets and possums provided a useful tool for reducing the cost of assessing infection rates in low-density wildlife populations.

Table 1. Summary of the host distribution of the most frequently recorded restriction endonuclease analysis (REA) types of *Mycobacterium bovis* in New Zealand wildlife and farmed livestock. Source data obtained from necropsy samples of livestock and wildlife in New Zealand, 1986–2011 (GW de Lisle, unpublished data). *M. bovis* strain identification was undertaken by REA typing of tissue samples provided under contract to TBfree NZ (formerly the Animal Health Board of New Zealand) as part of the tuberculosis surveillance and monitoring programme.

Strain characteristics			Number of <i>M. bovis</i> strains isolated from 1982–2011 from different hosts											
REA type	First isolated	Last isolated ^a	Cattle	Deer ^b	Cat ^b	Ferret	Goat ^b	Hedgehog	Horse	Pig ^b	Possum	Sheep	Stoat	Total
115	1983	2011	390	60	1	19				25	30			525
198	1982	2011	79	80	2	21				17	5			204
21	1982	2011	128	19	2	14				15	23			201
62	1982	2011	99	29	5	28				26	11		1	199
37	1982	2010	36	12	3	8	2	2		18	77	1		159
151	1985	2010	98	18	1	9				1	6			133
20	1996	2011	78	21		1				30			1	131
93	1991	2011	80	32		12				6				130
12	1987	2011	79	9	1	5			1	16	8		3	122
164	1982	2011	38	18	1	13				2	4		1	77
19	1985	2011	35	24		1				8	5			73
39	1989	1998	8			1	1			1	53	1		65
219	1989	2008	29	2	1	5	1			1	21			60
187	1989	2010	27	22		4					4			57
11	1983	2010	22	14		11				1	8			56
53	1982	2008	39	3	1					7	3			53

^a REA typing was superseded by variable number tandem repeat for typing *M. bovis* after 2011.

^b Includes both domestic and feral animals.

To circumvent the high costs of catching, sampling and processing large numbers of possums, and to overcome the limited sensitivity of this approach for detecting presence of TB in possum populations, the concept of sentinel-based surveillance for TB monitoring has been increasingly utilised. Sentinel-based surveillance was first suggested for monitoring TB in New Zealand wildlife by Nugent (2001) and has since been described for North American wildlife also (VerCauteren *et al.* 2008; Berentsen *et al.* 2011). A sentinel wildlife species is one which acquires infection primarily (or exclusively) from a sympatric wildlife maintenance host, or from the environment where the infected host was located. There are three key attributes of an effective sentinel; firstly the species is not itself a major part of the TB cycle but is predominantly a spillover host, secondly it is easily infected and remains alive in an infected state for months or years, and thus available for detection (Nugent *et al.* 2002), and thirdly it has a much larger ranging area than the maintenance host (i.e. it surveys an area covered by many possums). For example, in the Molesworth Station region of north Canterbury, New Zealand (42.2°S, 173.1°E) it has been reported that the average home range of wild pigs is approximately 17 times that of sympatric possums (Yockney *et al.* 2013).

Wild deer (Nugent 2005), feral pigs (Nugent *et al.* 2002) and wild ferrets (de Lisle *et al.* 2005a) have been described as sentinels for indicating the presence of TB in the New Zealand environment, with other lesser hosts such as feral cats and stoats sometimes also surveyed incidentally during surveys of the three main sentinel species. Of the main sentinel species, pigs have been shown to have the greatest overall utility followed by ferrets and then deer (Nugent and Whitford 2008). The high surveillance utility of pigs is due to the combination of a large home range (as described above), a propensity to readily acquire *M. bovis* infection by scavenging from tuberculous carcasses (Yockney and Nugent 2003) and a long post-infection survival time, which allows for an extended window of opportunity for TB detection (Nugent *et al.* 2015b). The latter is important because tuberculous possums (or their carcasses) are not available to be detected over such extended periods; a study by Nugent *et al.* (2013) demonstrated that, for wild possums artificially infected with *M. bovis*, 61% of the animals had died within 4 months, while Barron *et al.* (2011) demonstrated that *M. bovis* bacilli can remain viable in possum carcasses for only a matter of weeks, even under favourable environmental conditions. A previous study also referred to the survival time of possums following first detection of clinical signs of TB, indicating that this is usually <4 months (Norton *et al.* 2005).

The lesser but still high utility of ferrets as TB sentinels is also derived from a propensity to scavenge infected carcasses of possums and other wildlife (Ragg *et al.* 2000; Yockney and Nugent 2003). Ferrets are particularly useful as TB sentinels in farmed areas where feral pigs and wild deer are scarce or absent. Ferrets are widely captured and necropsied in such areas, both to reduce the risk of them transmitting infection to cattle, and to assess the rate of decline in TB prevalence in wildlife as a result of possum control.

Deer have also been used as sentinels, mainly in remote forested areas where pigs are difficult to obtain for disease monitoring and ferrets are absent. However, the rate at which deer acquire *M. bovis* infection from possums, presumed to be by aggressive inquisitive interaction with terminally ill possums (Sauter and Morris 1995), appears to be much lower than for the scavenger

species (Nugent and Whitford 2008). Moreover, wild deer are often expensive to obtain for large-scale surveillance purposes, so less use is made of them than pigs: over a 5-year period to mid 2012, TBfree New Zealand conducted more than 222 surveys of pigs, and necropsied almost 13,000 wild pigs as sentinels compared to 872 wild deer (Nugent *et al.* 2015b). In a few situations, such as on Molesworth Station, free-ranging cattle are used as sentinels for monitoring the trends in TB prevalence in sympatric wildlife (Nugent and Whitford 2008), but in this situation, the sentinels are subject to tuberculin skin-testing rather than necropsy to detect *M. bovis* infection.

Modelling of TB in possums

With the rapid decline in TB levels in livestock during the 2000s (Livingstone *et al.* 2015), it became clear that TB was likely to have been eradicated in many areas, and that some areas could begin to be declared free of infection in both livestock and wildlife. Initially a qualitative Expert System Approach was developed in the early 2000s to provide surveillance data-based guidelines under which an area could be declared free of TB following wildlife control. These criteria combined stipulations on disease status in livestock and wildlife, i.e. no confirmed locally acquired TB in livestock or detection of TB in the wildlife species under consideration for at least 5 years, with information about the history and quality of possum control, i.e. the possum population had been kept below its theoretical disease maintenance threshold for at least 3 years (Anonymous 2009). The approach was used mainly in places where infection in wildlife was confined to tens of thousands of hectares, rather than hundreds of thousands of hectares, and which were geographically isolated from the main infected areas.

An example of the successful implementation of this approach is the South Kaipara Heads region in the North Island over the three decades since 1980. This is a vector risk area (VRA) for bovine TB formed by the Kaipara Peninsula to the northwest of Helensville (36.68°S, 174.45°E). Land use in the region comprises farmland and plantation forest, which in the 1980s supported large populations of possums and wild fallow deer. Wildlife surveys conducted over the decade between 1977 and 1986 had identified possums with gross tuberculous lesions in South Kaipara (Livingstone 1988; Anonymous 2005). During regular livestock testing undertaken from 1984 onwards, 11/253 cattle and farmed deer herds from the region were reported to have diagnostic results indicative of *M. bovis* infection (Anonymous 2005). Consequently, possum control was initiated in 1987/88 over a >20,000 hectare area within the region. By 1989 further geographic spread of the disease in possums had been halted, again as determined by possum surveys (to identify animals with gross TB). Possum control was expanded to eventually cover an area of 36,500 ha by the mid-1990s, with intensive control from 1998/99 onwards that reduced possum populations below a residual trap catch index of 1% (explained below) over the entire area (Anonymous 2005). Along with simultaneous livestock diagnostic monitoring, necropsy surveys of possums and ferrets on farmland provided the greatest sensitivity for monitoring the decline in TB in response to possum control, and enabled the last livestock herd to be cleared of TB in 2003 (Anonymous 2005). However, wildlife surveillance sensitivity was lower in the 12,500 ha of land to the west of the region covered by

Woodhill Forest, so on-going monitoring of both possums and shooting of wild deer was continued, with necropsies conducted of regional lymph nodes in deer heads to identify gross tuberculous lesions at predilection sites. By 2004, TB was judged to have been eradicated from possums in the region, but on-going monitoring of deer as sentinels continued: over 600 fallow deer heads were examined between 2004 and 2011, with no gross lesions due to *M. bovis* identified (Anonymous 2013). Accordingly, the region's VRA status was changed from special testing to surveillance only in 2011, meaning that surveillance testing of the existing livestock herds in the area was reduced to once every 3 years. In 2013 a formal application was made to TBfree NZ to revoke the VRA status for the region, equating to regional TB eradication from the current 290 cattle and deer herds in the area (Anonymous 2013).

In the Kaipara Peninsula example, the declarations related to TB freedom were based on sampling strategies expected to detect disease at low prevalence in the wildlife populations under investigation, while accepting any inherent inaccuracies in estimated total population size, and hence numbers required for precise surveillance outcomes, i.e. "stopping rules". By the mid 2000s, it was realised that quantitative measures were likely to be required to validate qualitative assessments of the outcomes of population and disease control in wildlife, and to provide more objective justification for declaring an area free of *M. bovis* (Nugent *et al.* 2006). The difficulty was that although many surveys were failing to detect any TB in wildlife, this did not necessarily prove that TB was absent from the area. The likelihood that TB has been eradicated from a possum population depends on the duration, intensity and evenness of the reduction in possum numbers achieved by management. Monitoring of possum relative abundance trends, combined with an understanding of density-dependence in rates of *M. bovis* transmission between possums, was used to provide an epidemiological basis for making inference on the probability of *M. bovis* presence, given the level and duration of possum population control achieved. Building on initial deterministic non-spatial models (Barlow 1991a,b), subsequent spatially explicit modelling work indicated a high likelihood that population control programmes could eliminate TB by reducing relative possum abundance levels below a threshold trap catch rate of two possums per 100 trap nights (Ramsey *et al.* 2005). This rate (2%) is usually cited as a trap catch index and often expressed in terms of the residual trap catch index (RTCI) measured following possum control. Trap catch index is a commonly used index of possum relative abundance, which assesses the percentage of traps that capture possums when the traps are laid at a standardised frequency and spacing pattern for three consecutive nights.

While providing the basis of predictive modelling on which to base management decisions, the models cited above assumed a spatially uniform population reduction as a result of lethal possum control, which is difficult to achieve in the field, particularly with ground-based control. The risk of failure is most likely related to surviving clusters of infected possums, and control-induced changes in possum behaviour, reproductive rates and movement (Barron and Warburton 2010). It is not easy to detect small areas where there has been partial or total control failure. The RTCI method of assessing possum relative abundance after control proved useful in assessing the overall average effectiveness of control, but it is based on a low-intensity sampling strategy that provides only low spatial coverage and a coarse

indication of the evenness of control. This prompted the development, during the 2000s, of low-cost possum detection devices as an alternative and more cost-effective means of assessing changes in possum densities in response to control. Such detection devices included PCR Wax Tags (Pest Control Research, Christchurch, New Zealand; Ogilvie *et al.* 2006) and ChewCards (Connovation Ltd, Auckland, New Zealand; Sweetapple and Nugent 2011), with ChewCards in particular prompted by the need for a tool that enabled comprehensive detection and mapping of changes in relative possum abundance at large scales (Sweetapple *et al.* 2010).

While RTCI and possum detection devices remain widely used tools for assessing the effectiveness of possum population control operations, they lack the ability to quantitatively incorporate three important sources of information: (1) spatially heterogeneous population and disease dynamics on real landscapes; (2) surveillance effort that does not detect possums (i.e. no detection in traps or ChewCards); and (3) sentinel-derived survey data. These shortcomings led to the development of two novel quantitative models. The first is referred to as the Spatial Possum Model (SPM) and is a spatially explicit individual-based simulation model that incorporates animal behaviour and disease dynamics in response to population- or disease-control scenarios (Ramsey and Efford 2010). The second is the proof of freedom utility, which is a spatial modelling framework based on wildlife disease-surveillance data for quantifying the probability of disease eradication from a specified area (Anderson *et al.* 2013). These two models are now used in conjunction to provide managers with an objective means to declare an area disease free (see below).

Spatial possum model

Early mathematical models of the dynamics of TB in possums provided predictions of the level of possum control, through either culling, vaccination or sterilisation, required to achieve theoretical TB eradication (Barlow 1991a,b; 2000). However, such models were non-spatial and generally based on global transmission terms, which was adequate for predicting the dynamics of TB at large landscape-wide scales, but could not capture the effects of local transmission and spatial heterogeneities important at the smaller scales necessary to properly evaluate the effects of possum control. The SPM described by Ramsey and Efford (2005; 2010) was developed to account for this: it is an individual-based model that describes the utilisation of space by individual possums located explicitly in 2-dimensional space. Each individual is represented in the model by its sex, the location of its notional home range centre and the distribution of its home range utilisation (i.e. describing its use of space), modelled for convenience as a bivariate Gaussian distribution with scale parameter σ . In the SPM, *M. bovis* transmission occurs locally through home range overlap of infected possums with susceptible possums, and both natal and breeding dispersal also occur according to sex-specific dispersal kernels, thus allowing simulation of TB "spread" across a landscape. Environmental heterogeneity is incorporated using geographic information system habitat maps that represent the spatial distribution of possums at equilibrium density (local carrying capacity - K). Finally, to link the modelling outcomes to field data, the SPM also incorporates a model of the trapping process, which enables the densities of possums in the model to be expressed in terms of RTCI (Ramsey *et al.*, 2005). The SPM has been used to predict likely times to achieve TB eradication from possums under a variety of scenarios where non-

uniform (patchy) control is applied to heterogeneous landscapes (Ramsey and Efford 2005) and also to explore the cost-effectiveness of various control strategies using lethal control and vaccination (Ramsey and Efford 2010).

The most important initial contribution of this model was its prediction that reducing a possum population's relative abundance to below 2% RTCI on average, and maintaining it at this level for 5 years, would provide a 95% probability of TB eradication success. The model can also be used to predict the probability that TB has been eradicated in an area given the intensity, duration and spatial application of control. This requires compiling a control history for each management unit, using actual geographic information system maps of the distribution of possum habitat types, then simulating possum population and disease dynamics in response to the control history. A conservatively high prevalence of infection is usually assumed in the pre-control possum population, and the model then predicts the probability of TB eradication for each year after control.

While conceptually elegant, this approach relies on the accuracy of the epidemiological and demographic assumptions in the model, the accuracy and completeness of the control-history data (which are often fragmentary), and on the assumption that control has been applied evenly. Because of that high level of uncertainty, TB managers have chosen to use the model predictions as a statement of belief that requires empirical validation through actual surveillance aimed at detecting TB presence in possums.

Proof of Freedom utility

It is assumed that for most, if not all, areas of New Zealand possums are the only true maintenance host of *M. bovis* (Nugent 2011). Collection and modelling of TB surveillance data aimed at declaring areas TB-free are therefore focussed on assessing the likelihood that possums, if they are present, are still infected. The possum populations themselves are therefore surveyed directly, using trapping or cyanide poisoning, followed by necropsy and (often but not always) mycobacterial culture. In addition, or alternatively, spillover hosts such as pigs, ferrets and deer are now frequently killed as sentinels and necropsied as part of surveillance operations also, and their predilection-site tissues are excised and cultured. If *M. bovis* infection is found in any of these surveys, it is presumed by TB managers to indicate a high likelihood that disease is still, or was recently, present in possums, and further possum control is likely to be imposed. However, in most surveys of areas considered candidates for being declared free of TB, typically no TB is found; this presents an opportunity to objectively quantify the probability of disease absence from that possum population. To this end, the proof of freedom utility was developed to utilise, in combination, possum and sentinel disease-surveillance data to calculate this probability (Anderson et al. 2013).

Standard methodologies for calculating the probability of disease absence (Martin et al. 2007; Martin 2008) use individual animals as the sampling units and rely on estimates of population size, which are difficult and costly to obtain for wildlife. In contrast, the sampling unit for the proof of freedom utility is a spatial grid cell (e.g. 1 hectare) superimposed on the area of interest (Anderson et al. 2013). Both sentinels and host-capture devices (e.g. traps) are considered to have "searched" one or more grid cells for infected possums as a function of the home-range size of sentinels and possums. Accordingly, a probability of disease detection is calculated for each searched grid cell (unit-level sensitivity), which increases with increasing numbers of sentinels

surveyed and with increasing effort to capture TB hosts. The predicted probabilities of detection in each of the grid cells are aggregated to a system-level sensitivity for the entire area of interest, using a hierarchical approach that accounts for spatial coverage and relative risks (Caley et al. 2001; Martin et al. 2007).

The probabilistic nature of the proof of freedom utility has allowed surveillance effort using captured sentinels and deployed possum traps to determine the unit- and system-level sensitivities, even in the absence of possum captures (Anderson et al. 2013). A further extension is the incorporation of possum relative abundance data collected using interference detection devices, (Sweetapple and Nugent 2011). Although such devices cannot detect TB, a positive detection does indicate the presence of a possum, which is followed-up with the deployment of multiple traps. Since post-control surveys are conducted on possum populations at low density, this is a cost-effective surveillance method to mop-up spatial aggregations of survivors and to rapidly locate individuals if the disease persists (Sweetapple and Nugent 2009). Clearly, the widespread deployment of interference devices, that are generally rechecked once after 7 days, is less labour-intensive than nightly checks of traps, and a greater number of such devices can be deployed on any given night for the same cost and effort as a set number of traps. When the surveillance effort begins with an interference device, the probability of detecting TB in a grid cell, assuming an infected possum is in the area, is the joint probability of the occurrence of the following sequence of events: (1) the interference device is chewed by a possum; (2) the possum is subsequently captured in follow-up trapping; and (3) the diagnostic test (necropsy and culture) is positive. This joint probability allows managers to use data from chewed and not-chewed interference devices to make inference on the probability of *M. bovis* detection in any given area under consideration.

The proof of freedom utility uses Bayesian logic to calculate the probability that *M. bovis* is absent given no individual with TB is detected, and therefore requires a prior probability (Gelman et al. 2004) that the disease is absent from the area under consideration. Given that the utility uses surveillance data collected following possum population control, a logical source for the prior is the result of the SPM (above), which models population and disease dynamics following control. The integrated use of the two predictive tools (SPM and proof of freedom) allows wildlife disease managers to maximise the utility of available information related to the potential disease status in the area: population control effort; disease epidemiology; and surveillance of possums and sentinel species. However, both tools will always depend on parameter estimates obtained from independent studies, and so the accuracy of predictions is subject to any degree of parameter uncertainty (Anderson et al. 2013).

The above concern aside, model-based predictions of the probability of TB eradication are now being used to guide TB management decisions across increasingly larger areas of New Zealand. In such practical use, the decision-making framework based around the proof of freedom utility was implemented at large operational scales for the first time in 2013. It was a central decision-making aid contributing to the vector-risk area status being formally revoked for over 400,000 hectares in which the possum populations can now be considered free of TB (S. Hutchings,¹ pers.

¹SA Hutchings, Group Manager Programme Design and Farm Operations, OSPRI, Wellington, New Zealand.

comm.). On-going and future studies aim to refine our understanding of the parameters and the biological relationships that they represent, in order to increase confidence that the empirical outcomes of surveys and the predictions of the quantitative models used to assess TB freedom can be most accurately and reliably interpreted.

Modelling that integrates surveillance information from multiple sources to predict probability of TB persistence in possums as a decision-making tool

In addition to improving estimates of parameters used in the SPM and proof of freedom utility, there are two surveillance issues discussed here that require theoretical and practical development into the future: (1) increasing efficiency of surveying and declaring disease freedom over inaccessible and increasingly large areas; and (2) incorporating economic and political factors into the quantitative decision-making framework.

Progress towards the goal of a TB-free New Zealand requires the collection of adequate possum and sentinel surveillance data in order to reliably assess the disease status of TB endemic areas. To do this, surveillance must be capable of covering large areas at an affordable cost. An important area of research in the future will be the development of new models capable of incorporating biological and epidemiological information, together with multiple sources of low-cost surveillance data, to quantify the probability of disease detection (system sensitivity) in difficult-to-access areas. With the caveat that it may take several years to achieve a target probability of disease freedom, the modelling will work on the premise that by a specified date (or year) a TB-positive animal will either be found or the proof of freedom utility will reach the target level. Potential data sources to inform this modelling will include disease status of livestock in adjacent pastures, direct possum and sentinel surveys along forest/pasture margins, and data from sentinel animals (usually pigs) deliberately released into a surveillance area that can be tracked using VHF (very high frequency) and GPS (global positioning system) telemetry, and later recaptured to be tested for TB (Nugent *et al.* 2014). Additionally, and ideally, comparison of a range of freedom estimation model outcomes with predictions from sampling statistics would be undertaken on a research-basis across different habitat types, to provide more accurate descriptions of population size for the wildlife species (possums or sentinels) under consideration in each different area. Overall, such multiple data sources will have low annual sensitivities but will result in progressive increases in the probability of disease freedom.

While the coordinated use of the SPM and proof of freedom utility provides an objective probability of disease freedom, the establishment of the target probability for declaring success remains relatively arbitrary. Disease managers in New Zealand currently declare an area TB-free when the utility predicts a 95% probability of freedom. This is subjectively defensible, i.e. it is currently acceptable to stakeholders to be wrong 5% of the time on average, but it does not objectively balance the costs of making an incorrect decision. Decision theory needs to be utilised as a practical tool in the management process to optimise the selection of a stopping threshold (Regan *et al.* 2006; Rout *et al.*

2009). Such a framework will combine the potential monetary and political costs associated with surveillance and re-application of control, if TB freedom is wrongly declared, with the estimated probability of freedom to enable the expected cost and variance to be estimated for each stopping threshold. The result would be different optimal stopping values for each location and situation, and that either the overall outcome would be more rapid, or regional scale eradication could be achieved more cheaply.

In summary, the collaborative feedback loop between wildlife disease management and scientific inquiry has produced surveillance tools and predictive models that make *M. bovis* eradication an achievable goal for New Zealand, although there remains substantial scope for new, improved and more cost-effective systems within this objective. Continued collaboration will facilitate new advances and increased efficiencies at all levels of disease-surveillance inquiry: molecular; cellular; whole organism; population; and inter-specific dynamics.

Acknowledgements

This review work was supported by funding from TBfree New Zealand (formerly the New Zealand Animal Health Board), Project R-10735-01. We thank Dr Paul Livingstone (TBfree New Zealand, Wellington) and Dr Phil Cowan (Landcare Research, Lincoln) for providing critical comments on earlier drafts of this manuscript. Thanks also to Kirsten Vryenhoek of TBfree New Zealand for support with online referencing of contract reports.

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Submitted 30 October 2013

Accepted for publication 5 August 2014

First published online 29 September 2014