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Diseases, dilemmas, decisions—Converting epidemiological dilemmas into successful disease control decisions

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ABSTRACT

This paper describes 50 years of personal experience in dealing with a range of animal and zoonotic diseases at national and global level, using a series of selected examples to illustrate both the nature of the various dilemmas and difficulties faced, and the way in which they were solved using the tools and techniques that were available at the particular time. A major theme throughout has been the dependence on advancing computer technology, which initially allowed only simple analyses and modelling activities to be undertaken, but as computers have grown increasingly powerful, techniques such as Bayesian spatial regression have become available to the epidemiologist, making possible forms of analysis and disease modelling which had been mere dreams in earlier decades.

There is now a need to integrate these tools and techniques into a toolbox which allows both epidemiological and economic analysis to be applied to virtually any type of disease, thereby further extending the capacity of epidemiologists to solve even more difficult problems in the future.

1. Introduction

Over the course of 50 years involvement in applying epidemiological methods to solve complex disease control problems, I have watched the field of veterinary epidemiology and economics evolve from one where there were very few advanced tools and we relied heavily on our ability to observe and to think our way through problems, to the current situation where our toolbox is full of powerful techniques, but we still need to search for epidemiological insights and avoid the temptation to just crunch the numbers and believe the result must always be right. In this paper I draw on a chronological sequence of selected challenging disease situations in which I was involved as an epidemiologist, to illustrate the evolution of approach which occurred as we explored different ways of solving epidemiological problems, and how the combination of increasingly sharp tools and sharp thinking jointly provided the key to converting some very difficult epidemiological dilemmas into sound disease control decisions. This paper is a description of parts of my epidemiological journey, on which I have been accompanied by many excellent people, most of whom cannot be named in the text without losing focus on the subject, but most of them appear in the bibliography as co-authors. It is therefore, a personal perspective on a shared journey, a rare opportunity to look back on 50 years of disease control, and pass on some of the lessons I have learned.

2. The legacy of Calvin Schwabe

I had the good fortune to have several contacts with Cal Schwabe from 1969 onwards, and to gain the benefit of his vision and epidemiological ingenuity. Through this paper, I would like to recognise the extent of his contribution to our field. He was a leader in identifying and pursuing opportunities where epidemiologists could make a global contribution, and he was supportive of many younger colleagues in these efforts. In 1974, he was Chairman of the WHO/FAO/OIE Expert Committee on Veterinary Public Health, where under his leadership we laid out through the Report a vision of what has subsequently become widely known as one health. Although I was only 30 at the time and half the average age of the Committee members, he invited me to be the Rapporteur of the Committee, which meant we worked closely together on finalising the text of the report and subsequently pursuing its implementation. This gave me valuable exposure to his thinking and approach to achieving progress. He was also able to pick up

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new techniques and research opportunities from diverse sources, and I subsequently applied a number of the techniques I learned from him. I am therefore, very honoured to present the 2014 Calvin W. Schwabe Symposium address, honouring his contribution and demonstrating how I have applied similar thinking over my career of 50 years.

3. The contribution of John Wilesmith

I would also like to use this opportunity to recognise the very major contribution which John Wilesmith has made to epidemiology and particularly to successfully managing a series of very difficult disease dilemmas. Over the course of his career in the British government, John faced and dealt effectively with more epidemics and outbreaks than any epidemiologist should have to do, and his success in unravelling the epidemiological complexities of a number of major diseases deserves the highest praise. I collect epidemic datasets like other people collect stamps, and Britain has provided me with the outstanding gems in my collection. John has been very kind over many decades in offering me the opportunity to work with the datasets which he and Judi Ryan had built for each of the different diseases they worked on together. We have spent many hours together debating the interpretation of epidemiological evidence, and working out ways of answering epidemiological dilemmas. Some of these are illustrated in the examples below. John's greatest challenge and achievement was to identify the true cause of bovine spongiform encephalopathy (BSE), and guide Britain through to successful control of this disease, despite the endless supply of people who believed they knew better.

4. Core principles of epidemiological investigation

As I review 50 years of involvement in epidemiology, working with a long list of diseases in a variety of countries, I consider there are a few key factors which are influential on success in understanding and then controlling any particular disease.

1. Formulate all realistic epidemiological hypotheses and structures of the putative causal web for the disease, then progressively rule them out by evidence or experiment, including extensive use of thought experiments. While this seems self-evident, far too often people narrow the options too quickly into a preferred hypothesis and focus their efforts on proving this rather than disproving the alternatives.
2. Success comes from clarifying the framework of the causal web and hence understanding the underlying epidemiological pattern (even if imperfectly), rather than understanding specific individual processes more precisely, but failing to identify the weak points in the web, which facilitate control.
3. Having clarified the final causal model, identify as many intervention points as are realistic to apply, and design a robust and economically appropriate control strategy which is resistant to epidemiological uncertainties and unexpected developments.
4. Implement the chosen control strategy in ways which allow early experience to guide progressive adjustments.
5. Monitor progress using epidemiologically insightful surveillance procedures, and adjust the control strategy in the light of findings from the surveillance.
6. Be open to new information which may require a change in strategy, even if the information is unwelcome.

There is nothing novel about these points, other than the fact that far too often they are disregarded. In the following series of examples, I will bring out both successes and failures in resolving epidemiological dilemmas, and the critical importance of well designed investigations and analyses.

5. Bovine brucellosis

In the 1970s, Australia began a national brucellosis and tuberculosis eradication program. Both components succeeded, with Australia being declared free of bovine brucellosis in 1989, ahead of the expected date. It was a very expensive program, and the opportunity was taken to apply a number of epidemiological initiatives, particularly with regard to brucellosis eradication.

Up to that time, most data used in disease eradication programs was stored manually, or by the 1960s and 1970s records were stored on mainframe computers, with little or no direct access to the records by field staff responsible for the program. The decision was made to develop a novel approach for the Australian eradication program, and Dr Dick Roe Rob Cannon and I developed the Australian National Animal Disease Information System (ANADIS). This operated from 1977 on 18 minicomputers located at veterinary laboratories throughout the country, with a 19th at the national centre in Canberra, where we were based. Each computer had kB of memory, with the central computer having the luxury of kB. Hence programming had to be extremely efficient to process enormous numbers of records with such limited memory and very slow processors.

The focus of ANADIS was on providing an epidemiologically dynamic set of support services and management tools at the local level. Field staff entered data at each of the regional sites, and produced reports immediately. Very few people who used the computers had ever personally interacted with a computer before this. Integration of the system was by mailing of 8 in diskettes weekly from each laboratory to Canberra and back – making a true national distributed system in the best way possible in the 1970s. Key initiatives in the system were the authority given to field staff at local level to manage their part of the program and to analyse local data using epidemiological methods which were built into the software, while allowing national staff to monitor and evaluate progress across the country, and to solve problems as they arose. Rather than being a simple data repository, the whole system was designed to capture the epidemiological dynamics of the disease eradication program and allow monitoring of progress and detection of problems (Roe, 1979; Sykes, 1982; Andrews, 1988; Cannon, 1993). Because the system made extensive use of abattoir testing for brucellosis, the first key development was the implementation of unique property identification codes for all properties in the country, with each code including a check character. This is calculated when the code is established, such that it makes the entire code exactly divisible by 11, having converted letters to a numerical value. This system virtually requires local computer access so that errors can be corrected immediately, since the computer analyses all codes at data entry and reports incorrect codes. Early in the program the number of incorrect codes detected was worryingly high and very variable between locations (since all failed entries were stored and reported to Canberra), but as staff became familiar with the system the error rate dropped to a very low level. This simple system avoided large amounts of wasteful testing which would otherwise result from incorrect allocation of test results to a particular herd. All cattle sent for slaughter from a property were required to carry a tail tag with the code, and this tag accompanied the blood sample through the testing system.

The second important development was the establishment of a standardised classification system for herds based on their brucellosis test results, which could be accurately represented in computer code. Herds went through a sequence of steps in which infection was eliminated (if initially present), and freedom was

proved. An important category of herd in this classification was disbanded, which was missing from most other disease databases we looked at. The number of herds which go out of production temporarily or permanently is much larger than generally realised, and unless such herds are removed from the analyses, they produce serious biases in evaluations of progress, generally by making progress appear much better than it really is.

Monthly reporting of results used a transition matrix approach (Roe, 1979), in which the number of herds moving up the freedom ladder, moving down or staying in the same position was displayed in a simple tabular form, which was used throughout the country. Previously, each State had reported results in its own chosen way, and there was no consistency of interpretation across the country. Diagnostic reports to investigate differences in progress between different areas were available, and this led to a healthy rivalry in making progress towards eradication, as well as improved understanding of the factors influencing progress and the relative effectiveness of the different components of the program. A range of management support reports were also available to field staff, which reduced their record-keeping workload and assisted them to make quick and accurate disease control decisions. This combination of support services, and their immediate local availability, greatly assisted the operation of the brucellosis eradication programme, and facilitated rapid national eradication.

A second epidemiological initiative in the program concerned the use of computer modelling to guide decisions on key aspects of the eradication policy (Roe and Morris, 1978). At the time, true spatial modelling was impossible because of limitations on computer processing capability, and creative ways had to be found to represent the turnover of the animal population, the epidemiology of *Brucella abortus* infection, and the effect of control strategies. A Monte Carlo simulation model was therefore developed in which individual animals were represented by their infection status, vaccination status, serological status and age in years, with the model cycle being a year in length. Animals were clustered in dairy herds and beef herds with sizes matching the size distribution for the area of Australia being modelled. Herds were grouped into blocks which represented geographical districts, and movement of infection between pairs of districts was represented in a simple fashion based on their proximity to each other and the prevalence of infection in each district. To speed up processing time, a 10% sample of the true herd and animal numbers were simulated, then results were multiplied up to the full population. By current standards it was a structurally simple model with geography represented using a non-spatial but computationally effective method. All of the key epidemiological features were present and it was the best possible with the processing power available on a University mainframe computer at the time.

The model was used in conjunction with a national macroeconomic model to evaluate the economic benefit of the national brucellosis and tuberculosis eradication program (Conron and Rolfe, 1975), and was also used to evaluate a range of the main policy issues related to the eradication strategy. The decision which presented the greatest challenge to make wisely, and represented the largest risk to program success was when to cease Strain 19 vaccination of cattle (Morris, 1986), and whether to allow individual owners to make decisions, or to use either infection prevalence in a region or one of a number of other measures as the criterion on which to cease vaccination. The model showed that this decision was critically important because premature cessation would make it very difficult to eliminate infection entirely, while delayed or patchy cessation would delay proof of freedom due to low levels of false positive serological tests in non- infected vaccinated animals, and would substantially increase total costs for no epidemiological gain. It was concluded that vaccination should cease when the prevalence of test positive animals fell to 0.2% of the population in the region, and it should stop region-wide at that time, with no exceptions. The recommendation was adopted, and eradication was achieved earlier than had been expected, whereas countries which have adopted less clearcut policies on vaccination have faced delays in achieving certainty of eradication.

6. Discovery of bluetongue virus in Australia

In the 1970s, bluetongue disease in sheep was considered a major exotic disease risk to Australia, and there was a large investment in preparedness for a possible incursion of this disease, including the development of vaccines against the common strains found in Africa and the operation of a national arbovirus sentinel system in cattle herds across the country. At the time bluetongue viruses were recognised to be present in Africa and in North America, but were not known to occur elsewhere. All viruses isolated in the sentinel study were identified, and viruses which could not be identified by locally available methods were sent to the USA for characterisation. With hindsight, sentinel animals should have been tested serologically as well as virologically, but this had not formed part of the study.

In 1977, Australia was notified that a virus isolated from a sentinel animal in 1975 and submitted for identification to the Yale Arbovirus Unit in the USA, had reached the top of the identification queue and had been identified as a bluetongue virus of a novel serotype, subsequently named serotype 20. This caused great consternation in Australia, and we were faced with the problem that the virus had been present in northern Australia for at least two years, but nothing more was known. Urgent standardised serological surveys needed to be conducted across the country, but surprisingly we could not find an accepted documented procedure that was in a ready to use format for designing such surveys and determining sample sizes, so a document was hurriedly produced to guide field staff in collecting samples. It was later published as Livestock Disease Surveys (Cannon and Roe, 1982), and became the internationally accepted design document for disease surveys, which is still in use in various forms today.

As the survey samples were being collected and processed under extreme time pressure, it was necessary to consider policy options for national action and international negotiations. In 24 h, we developed and ran a model for evaluating the economics of eradicating bluetongue infection from the limited area then known to be infected on the north coast of Australia. However when the serological results came in from the various parts of the country, it immediately became clear that infection covered a large part of northern Australia and eradication was not feasible.

It progressively became apparent that bluetongue viruses had in fact been present in Australia for a very long time, creating a major epidemiological dilemma, the investigation of which changed substantially the understanding of this and other similar diseases at global level, despite the limited analytical tools then available. This required very politically sensitive discussions with some Asian countries, which led to testing of animals beyond Australia, and showed that bluetongue viruses are permanently endemic in the tropics and sub-tropics of the world. The factors that determine expression of clinical disease are principally the presence of susceptible sheep breeds (such as the Merino) and the host preferences and vector effectiveness of the *Culicoides* species which are endemic in the particular area. Disease is typically seen along the fringes of the vector distribution, where in favourable seasons vectors spread into areas where hosts are naïve to the agent. This pattern of occurrence was already well known for other vector-borne diseases in Australia and elsewhere, but none of us thought of it applying to bluetongue in Australia until it happened! We even had a known example in North America, where bluetongue virus was endemic in

the USA but absent from Canada, except in very warm seasons in the Okanagan Valley which lies just above the border, when the vector and the virus extend into the valley. But we did not think it applied to Australia, until we found that it did! It was a salutary lesson to me in the need to challenge untested preconceptions about diseases – all it would have taken was to test the sentinel animals serologically for bluetongue exposure, and we would have realised the true situation years earlier. We tried to do some mapping of the distribution of bluetongue serology to assist with market negotiations, but mapping software at the time was incapable of producing suitable maps of any epidemiological utility. Now Australia provides regularly updated bluetongue maps of the kind we could only dream about in the 1970s (http://namp.animalhealthaustralia.com.au/).

Some benefit did come from the event, because we had been unsuccessfully seeking major funding for several years for a high security laboratory in Australia (Australian Animal Health Laboratory, Geelong), and the design and planning of construction had all been completed, but building could not proceed for lack of funding. The Government instantly approved construction of the laboratory the same day that the discovery of the virus was made public.

7. Tuberculosis eradication in New Zealand

Brucellosis eradication in Australia and New Zealand proceeded broadly in parallel, and was successfully completed about the same time. Tuberculosis eradication in Australia also proceeded successfully and was completed by 1997. Infection was present in feral pigs and feral swamp buffalo, but epidemiological investigation showed that feral pigs were dead-end hosts, while buffalo were included in the eradication program since they were intermingled with cattle in northern Australia.

In New Zealand, early progress was made with tuberculosis control during the 1970s, but then areas began to be identified in which reinfection of herds was inexplicably common, and progress slowed and then reversed, with the number of infected herds climbing despite control efforts which should have been effective against infection in cattle. The culprit turned out to be the introduced Australian possum, *Trichosurus vulpecula*, which was eventually proved to be a reservoir host in New Zealand, although because of differences in the lifestyle of possums and other factors between the two countries, it never became infected in the wild in Australia. However it took thirty years from the first report of a possum with confirmed tuberculosis in 1967 until the epidemiology was fully resolved. Initial evidence of the importance of infection in possums (Cook, 1975) was strongly resisted by policy makers at the time, but as the evidence supporting the existence of a wildlife vector and the prevalence of tuberculosis-infected herds both rose steadily, there was eventual acceptance by both policy makers and later the farming community that the possum was responsible for most of the infection.

When I arrived in New Zealand in 1986 from the United States, the prevailing view was that possums contaminated pasture from externally discharging lymph nodes and cattle became infected by eating the pasture. If this was true then control was very challenging, but I was unable to find any existing evidence to support this hypothesis. I argued that the first step in understanding the epidemiology was a longitudinal study of an endemically infected possum population in contact with livestock, to resolve how infection was maintained and transmitted. Dirk Pfeiffer and I began this study in 1989, and a large number of people contributed to this and follow-up studies over the next 15 years. The findings have been published in over 100 papers and reports, and summarised in two review papers (Morris et al., 1994; Morris and Pfeiffer, 1995). Here, I will focus on the evolution of our epidemiological approach and the way in which the hypothesised causal web was built and tested. The first challenge was a method of diagnosis in the possum, since no diagnostic test was available. A previous attempt using radiography had failed, so we decided to use palpation and measurement of superficial lymph nodes in sedated possums, despite its expected low sensitivity and uncertain specificity. However, through repeated examination of the same possums, it proved to be a much better diagnostic method than we expected. The second challenge was to catch the possums frequently to examine them repeatedly, and that was achieved through a network of several hundred cage traps spread across the study site. A key tool was the molecular strain identification technique restriction endonuclease analysis (REA), which allowed us to analyse spatio-temporal patterns of occurrence of multiple different strains which infected possums and livestock on and around the study site, and was essential to proving some components of the causal web. This was my first opportunity to apply molecular epidemiology, which was then emerging as an important technology for disease investigation. The second technique which was crucial to understanding possum ecology and their interaction with livestock was radio tracking. Possums are nocturnal and move each night within activity areas up to a few hectares, but then return in early morning to a preferred denning area where they sleep in one of several dens they use, with a cluster of dens being shared by several possums. Dens are chosen to provide protection from weather and detection, and possums are very difficult to detect by visual investigation. Selected possums had radio collars attached, and their denning locations were regularly determined in order to understand the different social groups of possums on the study site. Possums were also geo-located frequently during the night by triangulation to estimate the size and shape of activity ranges.

Groups of cattle were kept separately in the open pasture area where possums grazed and the bush area where they denned, and tuberculin testing showed that only the cattle which had access to the denning area became infected. REA results linked cattle infection to infection in groups of possums which denned in the area where the cattle were grazing. However the nature of the dens meant that cattle did not have direct access to them, so must have become infected directly from the possums rather than from the environment. What also became clear was that tuberculous possums all denned in a few small areas within the total study site, typically with different REA types occurring in these local clusters, while possums denning in the rest of the study site did not become infected. Day and night visual and radio-location observation of possums showed that healthy possums were only physically active during the night, whereas terminally ill tuberculous possums could be found grazing and wandering in an incoordinated fashion during the day.

This led to the hypothesis that whereas there was little direct contact between cattle and healthy possums, tuberculous possums would attract the attention of cattle and their natural curiosity would cause them to investigate the possums and become infected via the respiratory route rather than through consumption of contaminated pasture. This was tested by sedating possums sufficiently to resemble the behaviour observed for tuberculous possums, and releasing them into a paddock with cattle. The cattle sought out the possum and investigated it in detail, including licking it all over. Similar but more vigorous interactions were observed between deer and sedated possums, whereas sheep (which are fully susceptible to tuberculosis but rarely become infected in New Zealand) showed no interest in the possum. Studies of dominance hierarchies in groups of cattle and deer showed that the dominant animals in a group were most active in investigating sedated possums, whereas low dominance animals undertook very little investigation. Five deer were then assessed for both dominance and level of interest in investigating sedated possums, and ranked from lowest to highest. They were then kept on the study site where

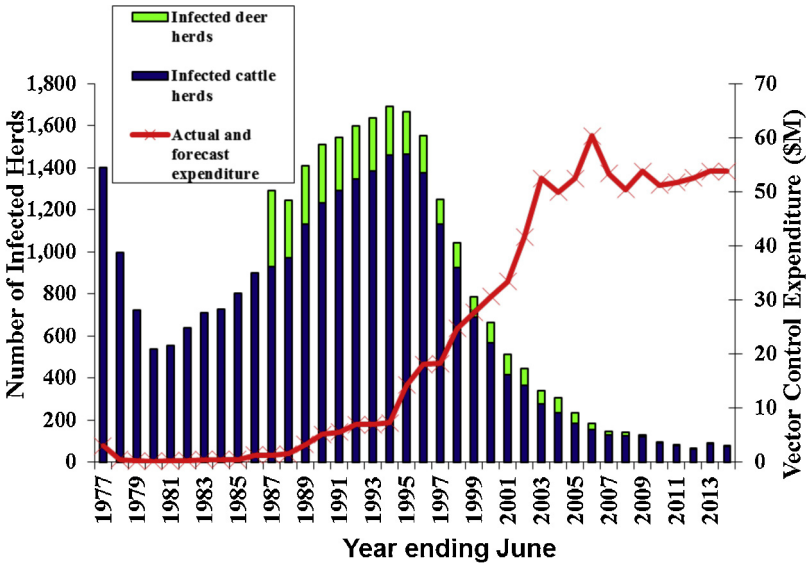

Fig. 1. Number of tuberculosis-infected cattle and deer herds in New Zealand 1977–2014.

they could come in contact with tuberculous possums. Four of the five became infected in sequential order matching their dominance score, while the lowest animal in the hierarchy never became infected despite an extended period of exposure. Thus, it could be concluded from this and other evidence that transmission of tuberculosis from possums to cattle and deer is via the respiratory route through direct physical contact, not by pasture contamination.

A second question which needed to be resolved was how transmission occurs within localised denning groups of possums, and how infection is maintained in such groups. As part of the longitudinal study, all possums on the study site were killed after several years and possums were then allowed to progressively recolonise the study site. During recolonisation, infection re-established in the same small denning areas as before, but with different REA types. Therefore, it was site suitability that was important, but not long-term environmental persistence of organisms. This was supported by a study of survival of *Mycobacterium bovis* in den sites. Further investigation of known similar sites around New Zealand (known as hot spots) showed that they were locations with relatively enclosed environments for denning, which would facilitate transmission of organisms, and favoured by possums so that populations were relatively dense. Transmission amongst possums occurs by social interaction including mating, and pseudo- vertical transmission from mother to pouch young, since these are marsupials.

A third question which needed to be resolved was the contribution of different species as maintenance, spillover and dead-end hosts for tuberculosis in New Zealand. At least 12 feral and wild species have been shown to become infected in New Zealand (Morris and Pfeiffer, 1995). If all had to be controlled, the problem would be very difficult. However investigation of infection in the various species both on the study site and in other locations showed that the possum was the maintenance host responsible for infection of cattle and deer herds, and that species such as feral pigs, weasels and stoats were spillover hosts from which infection disappeared if it was eliminated in possums. They played very limited roles in transmission of infection. Other species were found to be even less important, with one exception. Possum tuberculosis in New Zealand is concentrated in certain areas, with other apparently similar areas free of infection in possums. The common characteristic of affected areas is that they have substantial feral deer populations, and in one case transmission of tuberculosis from feral deer to a previously uninfected surrounding possum population has been documented. Feral deer are much more prevalent in New Zealand than in Australia, and my hypothesis is that feral deer are the underlying reservoir species in New Zealand, which have as a rare event infected surrounding possum populations in areas of high deer density, after which infection is maintained in the possum population without need for reinfection from deer. None of these various findings went unchallenged from various quarters, but as the parts of the causal web were progressively supported by results of specific epidemiological studies, resistance to the overall explanation of the disease declined.

Having put together the epidemiological story, it was then necessary to convince the farming community of its truth and to encourage their cooperation in intensified control efforts. To do this, talks were given to communities throughout the country. Interestingly, the most convincing evidence to local people was our videos of sedated possums being investigated actively by cattle and deer, but not by sheep. They could see how infection would spread, and many had seen possums behaving unusually in daylight, but had not recognised their significance.

Tuberculosis control has since the 1990s received heavy investment in New Zealand and achieved dramatic reduction in the number of infected herds, as shown in the following Fig. 1 provided by Dr Mark Bosson, epidemiologist for the TB control program.

The graph shows the number of known infected cattle herds from 1977 and the number of infected deer herds from 1987 (when deer testing began), and demonstrates the reversal in infected herds which began in 1980 and continued to a peak of over 1600 infected herds in 1993, and the rapid decline since then as the current control strategy focussed on intensive possum population control took effect, with under 100 herds currently infected.

The research applied a wide range of investigative and analytical approaches, many of which had only recently become available as computer technology and molecular methods advanced, resulting in a far more optimistic outlook for control, which has been borne out by subsequent experience. There remains an open question as to whether population control alone will meet national control objectives, and this is a subject of continuing debate. BCG vaccine was shown in our research to protect possums against challenge (Corner et al., 2001, 2002a,b), and vaccination could offer a valuable adjunct to population control, but has not so far been adopted.

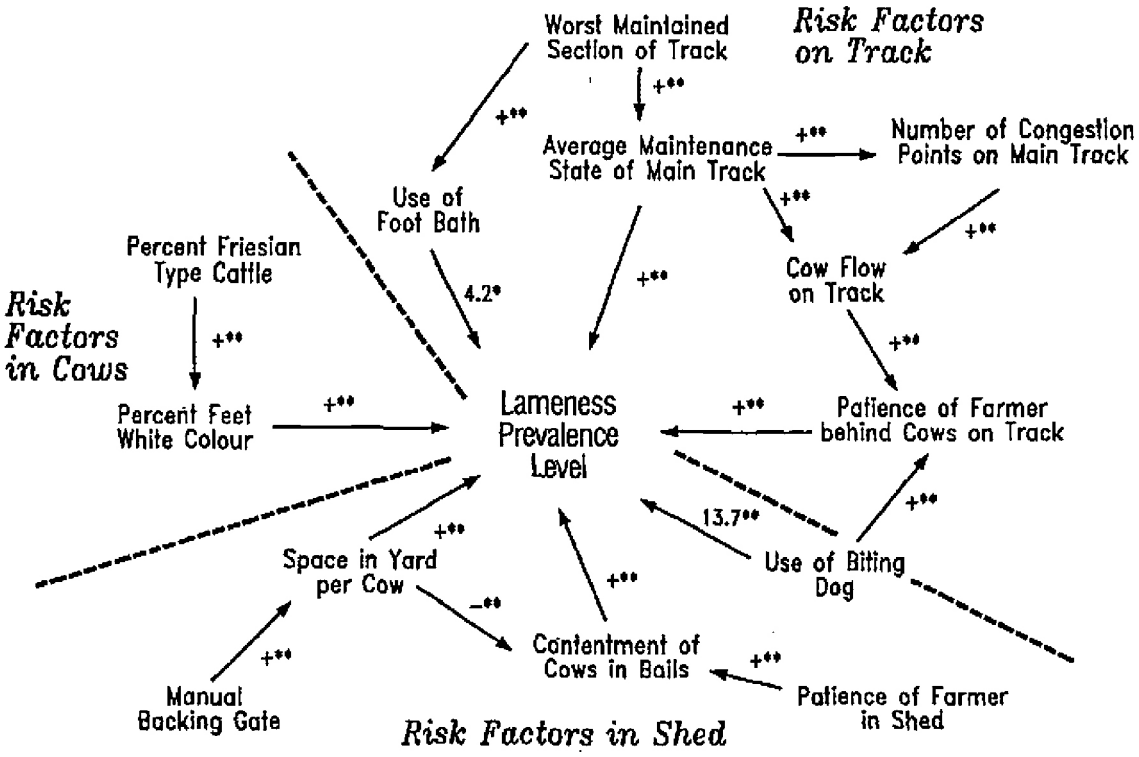

Fig. 2. Final path model for lameness in dairy herds.

(From Chesterton et al., 1989)

8. Lameness in dairy cattle

I have chosen this example of the successful application of epidemiology at farm level from our many farm-based disease investigations, because it links to Cal Schwabe, and needed a very different approach from national disease investigations. Shortly after I arrived in New Zealand I was approached by a veterinary practitioner, Neil Chesterton, who had collected large amounts of data about dairy herds in his area which had lameness problems, but he had no idea how to analyse it. I sent him away to collect equivalent data on an equal number of herds which did not have lameness problems. Several years earlier, Cal Schwabe had sent Mike Burridge to visit me in Australia, when he was on his way to investigate Cal's favourite disease, echinococcosis, in New Zealand. New Zealand had comprehensive records of its hydatid control program, and Cal had arranged for Mike to have access to the data, from which they subsequently published a series of papers. This included the use of path analysis (Burridge et al., 1977), which Cal had learned from social scientists, and I had been looking for several years for a study to which I could apply the technique. The lameness study provided a suitable example, and Dirk Pfeiffer and I applied it to the data, with the following result, as shown in Fig. 2 (Chesterton et al., 1989).

Dairy cows in New Zealand commonly walk quite long distances between pasture and milking shed, and factors on the track can be quite important. The issues which were included in the final path model were epidemiologically plausible and helpful in explaining why some herds are prone to lameness problems. A particularly interesting factor with a very strong effect was the use of a biting dog to bring cattle in for milking, as distinct from a dog which simply barked. When cattle are walking along a track in a large herd, they keep their heads down to observe where to position their front feet, and their back feet land in exactly the position where the front foot had been previously. Therefore, if cows are able to move at their own pace, they will position their feet to avoid injury. Barking dogs behind the cows allow this careful form of walking. However, if the dog is biting at the heels of the last cows, they will push forward to escape, and most of the cows in the group will raise their heads to monitor for the biting dog, and so will no longer be able to position their feet carefully. Hence the strong effect of a biting dog on the occurrence of a lameness problem.

Subsequently a series of further studies was undertaken to understand lameness more fully at both cow and herd level (Tranter and Morris 1991, 1992; Tranter et al., 1991, 1993; Sauter-Louis et al., 2004). The biggest problem in understanding and managing lameness is that there are no investigational procedures equivalent to the laboratory diagnostic tests used for other diseases. Without ways of assessing risk factors for lameness at the cow level down to the digit level, it is difficult to examine the epidemiology of the disease. We therefore, invented methods for measuring a range of hoof factors such as hardness, moisture level, elastic modulus, compressive strength, resilience, colour and sole concavity, using devices borrowed from totally unrelated fields (such as measuring drying of paint) and adapted for studying cows' feet. We also developed methods for measuring the rate of wear of different parts of the sole surface, which is a challenging problem. Because lameness is a clinical sign rather than a specific disease, it was also necessary to develop a classification system for hoof lesions in both clinically lame and non-lame animals, and it became clear that there were substantial levels of hoof damage in many cows that were not clinically detectable as lame, but had similar lesions to the clinically lame animals – so the problem was wider than just the worst affected animals. With the goal of finding a treatment which would make hooves more resistant to lameness, daily formalin footbathing and application of a commercially available hoof protectant were tested separately and jointly, but both failed to reduce lameness and showed very little effect on hoof characteristics such as hardness and moisture level.

The approach which has been effective and has resulted in substantial reductions in lameness levels in dairy herds across New

Zealand has been to work with farms by changing track design and construction, and especially the behaviour of milking staff, so that they better understand causes of lameness and minimise risk factors in handling the herd. The epidemiological evidence on factors influencing variation in amount of lameness between herds, and ways of reducing risk factors, has been very beneficial.

9. Foot and mouth disease modelling

One of my career-long interests has been the development of computer modelling methods for undertaking epidemiological and economic analysis of disease control strategies. As a new graduate, I studied economics, pure mathematics and mathematical statistics to gain the necessary skills to develop models, and I published my first paper on modelling before the technique was widely known (Morris, 1972). I initially expected to use differential equation modelling, which was then and remains one of the principal accepted modelling approaches. However, as I worked on this approach I realised its severe limitations in providing a biologically sound representation of an animal population and its interaction with the disease agent, and I switched to Monte Carlo simulation modelling, which enabled me to satisfy my epidemiological expectations about the capacity of a model to be biologically accurate. The debate about the relative merits of different modelling methods goes on forever, but I am personally satisfied from my assessment of the published literature and comparisons between real epidemics and the predictions of different modelling methods, that Monte Carlo modelling produces findings which are of great practical value in the management of disease control programs.

The evolution of our modelling work on foot and mouth disease provides an illustration of how the models have been useful. The first foot and mouth disease model we constructed in the 1970s ran on the ANADIS minicomputers described earlier, and was called Exotica. It consisted of a square grid of farms, with disease spread occurring according to evidence from the 1967/68 FMD outbreak in Britain, and control procedures based on experience of people who had been involved in that outbreak. It was purely intended as a training tool to help veterinarians recognise the challenges of controlling an FMD outbreak, and to give them an opportunity to make management decisions in the face of an outbreak, then see the outcome of their decisions. We made it freely available, and it spread like an epidemic through veterinary services in various parts of the world, and continued to be used long after we had moved on to more spatially realistic modelling strategies.

Ten years later it was possible to use spatially realistic representations of the real geography and farm structure of a country, and model foot and mouth disease on the true population of any country. As part of a larger project to develop the EpiMAN system for emergency disease control (Morris et al., 2002), the Interspread model was constructed with true geographical representation of farms, represented either as shape files or if necessary as points. The model has each of the disease transmission processes represented explicitly, and disease control and surveillance measures can be specified in epidemiologically realistic ways through a graphical user interface. Importantly, the random number generators for all processes within the model are independently seeded, so for example the same epidemic may be run many times with different surveillance and control policies. Over the 25 years since its initial development, the model has been enhanced progressively, first in the form of Interspread Plus (Stevenson et al., 2013), which can deal with any contagious disease instead of being limited to FMD, and now in the form of HandiSpread, which can deal with transmission of a zoonotic agent to people and has built in economic analysis. It is currently being expanded to allow it to deal with non-contagious diseases such as vector-borne and food-borne infections.

The model was used daily during the 2001 FMD outbreak in the UK (Morris et al., 2001), with modelling taking place in New Zealand after all data had been entered in London for the day, taking advantage of the 12 hour time difference. There was intense controversy during the 2001 outbreak about the use of models and the appropriateness of some of the recommendations from other models which were vigorously promoted, but never actually implemented on a substantial scale. Epidemiologists who were directly involved in the control program concluded as follows (Mansley et al., 2011):

"The InterSpread model was used by MAFF/DEFRA on a daily basis during 2001 to monitor the epidemic size, duration and spatial spread. The model includes accepted veterinary assumptions, such as animals being infectious from just before the appearance of clinical signs until slaughter; excretion rates being variable depending on the stage of disease; the species affected; the occurrence of an on-farm epidemic, and various farm factors. It also allows transmission by specific contact routes and considers the effects of having control measures in place, e.g. DC assessments and contact tracings data, allowing greater parameter flexibility. There was a cautious interpretation of its output, recognising the dynamic and often unpredictable nature of FMD infection, although the results closely matched field observations, thus promoting confidence in its output. For example, the conclusion by field staff that disease spread was being maintained by mechanical means, and in particular by the movement of contaminated personnel and vehicles, was supported by the output of the InterSpread model, and the need for the heightened biosecurity measures was eventually adopted in the 'Blue Boxes'."

The last of these points arose from the fact that whereas earlier in the epidemic forward predictions from InterSpread matched closely with subsequent field experience, from about the date when Tony Blair announced that the delayed national election would now proceed, InterSpread kept predicting eradication but the epidemic dragged on. It appeared that people in remaining affected areas now believed that the disease was under control, and relaxed their compliance with control measures. When model parameters were adjusted to take this reduced compliance into account, model results again matched field reality, and this provided support for the imposition of the intensified controls known as the 'blue boxes', following which the disease was promptly eradicated as predicted by InterSpread.

InterSpread Plus has been used in a range of countries with various diseases, both as a policy evaluation tool and to investigate actual epidemics (Jalvingh et al., 1999; Bachmann et al., 2005; Yoon et al., 2006; Boklund et al., 2009; Ribbens et al., 2012; Longworth et al., 2014). While it is important to remember that all models are representations of reality rather than reality, they can give valuable insights by representing complex interactions in ways that cannot easily be replicated through thought experiments, and on several occasions my models have shown me the errors of my thought experiments.

10. Bovine spongiform encephalopathy

In the 1990s, emergence of bovine spongiform encephalopathy created major problems in the United Kingdom, and subsequently to a lesser degree in both affected and unaffected countries around the world. Epidemiological methods rapidly identified both the cause and an appropriate initial control strategy (Wilesmith et al., 1988, 1991, 1992a,b; Wilesmith, 1990, 1991, 1994), but the disease subsequently threw up several waves of epidemiological dilemmas, reaching tsunami level when variant Creutzfeldt Jakob disease was first attributed to the BSE prion (Will et al., 1996). Prion diseases provide ample scope for controversy and dispute, and had it not been for the rigorous application of epidemiological methods this disease would probably have caused even more serious problems.

There was a comprehensive file of all cases of BSE in Great Britain, but the long incubation period produced a number of problems in testing epidemiological hypotheses about the disease. We worked with John Wilesmith and Judi Ryan to minimise biases in the data set, and develop methods of analysing the large but difficult volume of data. Because exposure typically occurs in calfhood but disease expression occurs in adulthood, animals which were recorded as having moved from their birth herd to the herd where they were diagnosed, were relocated for analysis back to their natal herd, and animals which had uncertain natal herd and/or birth date were excluded from some analyses. Consideration also had to be given to the fact that the dose which animals received varied over the course of the epidemic, and this influenced the incubation period. A further factor which had to be considered was that the first ban on use of meat and bone meal as a cattle feed had loopholes related to potential cross-contamination between pig and poultry feed and cattle feed, so that the animals born after the bans (known as BABs) had higher but geographically variable exposure than animals born after the reinforced bans (known as BARBs). A further intriguing issue was that although it became accepted that variant Creutzfeldt–Jakob disease was caused by the BSE prion, the gradient of vCJD cases from south to north in Great Britain was the exact opposite of the gradient for BSE cases.

By the late 1990s, Bayesian spatial regression had become available for use with large data sets such as BSE cases, and we wanted to apply it, but we faced a number of difficulties. Firstly, some of the variables of interest were only available at county level in Great Britain, but the numbers of BSE cases and the cattle population at risk were so variable between counties that county was a problematic spatial unit on which to base a Bayesian analysis. The smallest administrative unit for which BSE case data and animal population data is available in Great Britain is the parish, but there are 12,277 of them, which was far too many to treat them all separately in the analysis. We therefore invented the equi-cow district as a spatial unit. This was a spatial amalgamation of contiguous parishes within a county in to analytical units we called districts, to achieve about 20,000 cows per district. This gave us 178 equi-cow districts suitable for Bayesian spatial analysis, after Mark Stevenson had done the painstaking work of defining the districts.

After examining the overall distribution of BSE cases (Stevenson et al., 2000a,b; Wilesmith et al., 2000), Bayesian spatial analysis with a mixed effects (Poisson) model and also a random effects model were used to evaluate the influence of various factors before and after the imposition of the initial ban on feeding meat and bone meal (MBM) to cattle in July 1988. This showed the expected south to north decline, and a high pig to cattle ratio was associated with a mild increase in risk before the MBM ban, and a higher increase in risk after the MBM ban, when it was suspected that cross-contamination of cattle feed by pig and poultry feed was reducing the effectiveness of the ban in areas where pig and poultry density was highest. Only pig density could be used in the analysis, because a high proportion of poultry were recorded as being in central London, where the companies had their headquarters! An important finding was that a high ratio of sheep to cattle (measured as mutton production) was protective rather than a risk factor, both before and after the MBM ban. The evidence suggesting that scrapie is the source of the BSE agent is largely circumstantial, and an unpublished analysis we have undertaken of the very early cases of BSE suggests a possible focal starting point in the south west of Britain, rather than a geographically dispersed initiation.

11. Bovine spongiform encephalopathy surveillance

As there was increasing recognition that trade in meat and bone meal had moved infectious material to many other countries, it became necessary for known infected countries to monitor BSE infection levels, and for uninfected and uncertain countries to provide evidence of freedom. Four different surveillance procedures were widely adopted – examination of clinical suspects, examination of animals which died on farm from an unknown cause, casualty slaughters, and healthy slaughter stock. However the combination of long incubation period, the fact that diagnosis was only possible after death and the differences between the different surveillance procedures in the age profile of both positives and negatives, meant that extrapolating from test data on dead animals back to the BSE status of the live animal population was not a simple process, and different countries were interpreting their data in different ways, which made comparisons unreliable. Each of the tests also has a substantially different total cost, which means the cost-effectiveness of allocating resources to different components of the surveillance strategy needs to be taken into account.

The European Commission requested help in developing a standardised system of interpreting surveillance data across all EU Member States and allocating test resources to the different components, which we termed surveillance streams. John Wilesmith asked us to share the work with him, and we undertook a programme of research to produce a solution to this very thorny problem, and then ran training courses to teach people how to use the analytical procedure we developed. It took considerable discussion to come up with a technique which was statistically and epidemiologically valid and also could be understood by most users. Our first proposal met the first two criteria but initial reviewers had difficulty with its complexity. We eventually developed a system which took advantage of work we were doing on the application of portfolio theory to risk-based surveillance (Prattley et al., 2007b,c) and analysed data separately for each age cohort of animals and each surveillance stream, since the age distribution of animals being tested through each surveillance stream was different. While the epidemiology and statistics were quite complex, they were built into a spreadsheet structure BSurvE (Prattley et al., 2007a,b,c) which enabled users to enter relatively simple data sets and get the information they needed to meet individual national needs for surveillance decisions, depending on the BSE status of the country. A simplified version of the system was subsequently adopted by the OIE, and has been used globally to manage BSE surveillance as global control has progressed.

12. Global eradication of rinderpest

Rinderpest has been a major scourge of cattle since at least Biblical times, and caused repeated large scale epidemics in many parts of the world, with exceptionally devastating effects in Europe over several centuries. Development of an effective vaccine provided a major reduction in outbreaks in regions where it was methodically used. Eradication became a technical possibility, but early efforts to achieve area freedom from rinderpest in various parts of the world and especially to maintain freedom were prone to breakdowns, usually when commitment was not sustained – and there was no reliable surveillance system to detect breakdowns early enough. From 1960 to 1976 the multinational Joint Program 15 (known as JP15) for rinderpest control in Africa was initially very successful across 22 countries, of which 17 were infected with rinderpest. However when responsibility for funding and undertaking vaccination was passed back to the countries, many did not fulfil their obligations. By 1979 only Sudan admitted the existence of rinderpest, but in reality the lack of an effective surveillance system meant that the freedom claimed by some of the other countries was a mirage. When epidemiological circumstances created the right conditions, the disease swept back across Africa and the gains of JP 15 were largely negated. Following this failure, I chaired an

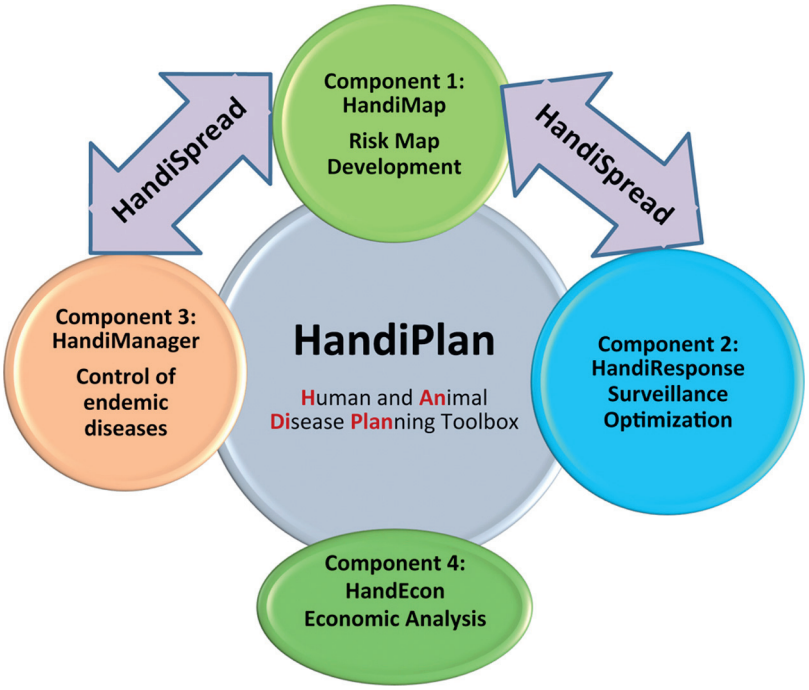

Fig. 3. Components of the HandiPlan epidemiological and economic toolbox.

OIE Expert Consultation on Rinderpest Surveillance Systems in 1989, at which we designed a multi-stage pathway for achievement of national freedom from rinderpest, based on progressive intensification of surveillance through stages of provisional freedom from disease, freedom from disease and finally freedom from rinderpest virus infection. These steps were subject to international verification and provided a framework for countries to follow in eradication of rinderpest. New funding was provided to various regions of the world to support their surveillance and control efforts, and progress was more rapid than expected, culminating in the declaration of global freedom in 2011, only the second disease in history to reach this goal (after smallpox). In fact, only a few countries completed all the stages in the pathway, but the pressure applied through the structured approach to surveillance and control across the various regions of the world through the implementation of the pathway was completely successful in preventing breakdowns of the kind which had occurred in JP 15. At the time we designed the pathway we were very uncertain that countries would accept international scrutiny of their control activities, but in fact our report was accepted without difficulty, and the same strategy has since been adopted for other diseases. In the 1980s, there was still a widespread view among countries that whatever they reported about their disease status was the truth which should not be disputed, even though it was widely known that the validity of reports varied greatly between countries. The introduction of an internationally monitored epidemiologically structured surveillance system for a disease was therefore a novel development in the 1980s, although this has changed very rapidly in subsequent decades as the need for such systems and the benefits they provide in international trade and global disease control were rapidly accepted, assisted by the occurrence of several global disease epidemics, of which BSE was the most difficult and influential.

13. Responding to current emerging diseases

The period since 2000 has been the era of emerging and re-emerging zoonotic diseases. Several have caused significant epidemiological challenges and have had global impacts, including SARS, multiple novel influenza viruses and most recently Ebola virus, while a much longer list of diseases have caused problems at regional levels. A notable feature of these disease outbreaks has been their capacity to cause secondary economic and social disruption on a scale well beyond the primary impact of the actual diseases, often due in part to enhanced spatial dissemination of misinformation causing epidemics of angst. This has however had the benefit of drawing together people involved in human health, animal health and wildlife health to form valuable collaborations under the umbrella concept of One Health. The developments of recent years would have delighted Cal Schwabe, as they move a long way towards fulfilling his vision.

There remains much to be done in fully utilising the synergistic framework which has been established. With support from World Bank and the European Commission, we have developed postgraduate training programs which bring medical doctors, veterinarians and wildlife specialists together in a joint educational framework involving extensive interdisciplinary collaboration, and the program has so far involved over 100 people from nine countries in Asia. A core part of this program has been the implementation of epidemiological investigation strategies for diseases of importance in project countries.

In order to assist epidemiologists and policy makers in the countries where we are working to apply both epidemiological and economic techniques quickly and effectively to solving their disease control problems, we are currently bringing together software tools which we have developed separately into an integrated toolbox (Fig. 3) we call HandiPlan (Human and Animal Disease Planning Toolbox). The mapping tool uses both satellite-derived and national data layers to formulate a risk landscape for the country which represents the influence of environmental and demographic data on known or expected occurrence of disease, and then this risk landscape is used by the modelling software HandiSpread to simulate disease occurrence, taking into account spatial variability in transmission probabilities across the risk landscape. For endemic diseases, HandiManager uses the economic tool HandEcon in con-

junction with the results of modelling in HandiSpread to evaluate the expected economic and epidemiological benefit of alternative control strategies, while for diseases which are not present but are at risk of occurring, HandiResponse uses the same tools to develop an optimal risk-based surveillance portfolio to detect any incursion of the disease. At present the tools can be used for contagious diseases, and the next stage will involve extending their application to food-borne, vector-borne and other non-contagious diseases. The vision is to use these tools to facilitate more comprehensive and rapid evaluation of disease control options, so that better decisions can be made in the future than were made in the past.

14. Discussion

In the last 50 years, epidemiological and economic techniques to support disease control activities have advanced very greatly, and the objective of this paper is to illustrate these advances through a selected series of examples of disease investigations in which I have played a part, and in which various dilemmas and problems were faced and had to be dealt with – usually but not always successfully. In the early examples our techniques and tools were relatively primitive by modern standards, yet we managed to achieve success in most cases. Gradually the techniques became more powerful but the dilemmas also became more difficult, so I never felt that the problems were getting any easier to solve.

There are still many epidemiological conundrums and dilemmas to be investigated, but with the growth in both the number of epidemiologists and the number and power of the tools at their disposal, I hope that progress will be faster in the next 50 years that it was in the last 50.

Acknowledgments

The investigations and the thinking about disease investigation and control which I have summarised in this paper are the joint work of a large number of people with whom I have had the privilege of undertaking research over the last 50 years, and the work would not have been possible without their involvement, since they did most of the hard work. They are too numerous to list, but their contributions are acknowledged and greatly appreciated.

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