

# Dairy Sessions

Moderator: Herman Barkema

## Epidemiology of Endemic Infectious Diseases — Accept Endemicity or Eliminate?

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### Abstract

Endemic infectious diseases (such as mastitis, infectious bovine rhinotracheitis (IBR), Johne's disease (JD), or tuberculosis in cattle) are common causes of disease in livestock. They affect health and well-being and reduce the economic potential of each animal, herd and industry. Endemic diseases exhibit necessarily complex epidemiologic and pathogenic behavior; those that exhibit less complex behavior have generally already been controlled. We are still far from fully understanding the epidemiology and pathobiology of many endemic infectious diseases. To improve animal health through control of infectious disease, we need to understand endemic disease persistence.

The aim of this paper is to provide an insight into some of the mechanisms for disease persistence. We argue that heterogeneities in hosts and pathogens, and survival of the organism in the environment, play an important role in maintaining endemicity. The options to either eliminate or control endemic infectious diseases are explored using some common infectious disease examples. Finally, approaches to optimally manage infectious diseases of livestock are discussed.

**Key words:** bovine endemic infectious disease, persistence, control, populations,  $R_0$

### Résumé

Les maladies infectieuses endémiques (telles que la mammite, la rhinotrachéite infectieuse bovine [RIB], la paratuberculose ou maladie de Johne, et la tuberculose des bovins) incommode couramment le bétail. Elles affectent la santé et le bien-être de tous les animaux atteints, réduisant leur potentiel économique et celui de toute l'industrie. Les maladies endémiques manifestent intrinsèquement une épidémiologie et une pathogénèse complexes, les plus simples d'entre ces

maladies étant généralement déjà contrôlées. Nous sommes encore loin de bien comprendre l'épidémiologie et la pathobiologie d'un bon nombre de maladies infectieuses endémiques. Si l'on veut améliorer la santé des animaux en combattant ces maladies, nous devons comprendre leurs mécanismes de persistance, ce dont cet article donnera un aperçu. Selon nous, l'hétérogénéité de l'hôte et de l'agent pathogène, ainsi que la survie de ce dernier dans l'environnement, jouent un rôle important dans le maintien de l'endémicité. Nous discuterons aussi du choix entre l'élimination ou le contrôle des maladies infectieuses endémiques en prenant des exemples de maladies infectieuses courantes. Enfin, nous discuterons de stratégies de gestion optimale de ces maladies du bétail.

### Introduction

Infectious diseases may be divided into those infections that are endemic in a country or region and those that have been eliminated. An infectious disease is endemic when it persists in a population. A pathogen is exotic when it is absent from a population either because it has never been introduced or because it has been eliminated from a population: global elimination is defined as eradication. For eliminated infections, it was at some point decided to control this infection and this control eventually resulted in elimination. Once eliminated, all animals within the pathogen-eliminated group are susceptible, so elimination requires a permanent control strategy unless global eradication occurs. Reintroduction of such eliminated infections often results in epidemics.

Much elimination of infectious diseases occurred even before their bacterial or viral causative agents were discovered. Elimination occurred through observation and a stamping-out policy of diseased individuals. New introductions of disease were avoided through observation of clinically diseased animals. For example, it was

noted that approximately 70% of cattle that accompanied the British armies to feed the soldiers died of cattle plague. It was proposed that Great Britain should eliminate cattle plague by avoiding contact with cattle and cattle products from other (plague-infected) countries.<sup>5,14</sup>

In contrast, endemic infectious diseases are continuously present in the population and elimination does not appear feasible, or is of no particular interest. In some cases, endemic infectious diseases may be very difficult or impossible to eliminate. Examples would include *Listeria*,<sup>36</sup> *Campylobacter* and very likely *Mycobacterium avium subsp. paratuberculosis* (MAP).<sup>31</sup> Some infectious diseases lend themselves well to elimination. These infections are typically readily diagnosable, only transmitted between susceptible individuals and relatively easy to treat or eliminate by culling. Economic reasons will eventually decide whether such infections will be eliminated. For example, *Streptococcus agalactiae* infection of the mammary gland shows all the above characteristics,<sup>1</sup> but will typically not be eliminated from a country or region because of its relative low economic impact.

The distinction between endemic and eliminated infections is herd, region or country specific. Some infections are eliminated in certain regions but endemic in others. For example, foot-and-mouth disease is eliminated in most western countries but endemic in many countries in Africa.<sup>24</sup> Within the western world, some regions have eliminated bovine tuberculosis, while it is endemic in Great Britain and in the deer population in the state of Michigan. Similarly, some countries (for example, Denmark) have eliminated IBR, while it is endemic in most other countries.

In this paper, we aim to present the distinction between endemic and epidemic (introduction after elimination) infections. We will argue that elimination of endemic infections requires efforts beyond what may be expected from classical modeling studies. We will discuss the necessary arguments to be considered to decide on control or elimination of endemic infectious diseases.

## Repeated Introduction versus Persistence

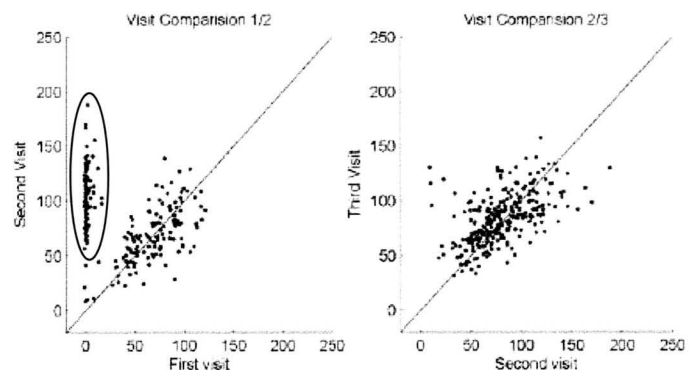
### Repeated introduction

When considering control of endemic diseases we need to consider routes for pathogen introduction and routes for persistence. Classic routes include introduction of an infectious animal, animal product, wind or fomite. The routes of introduction are similar for exotic and endemic diseases, but we see them less clearly in endemic diseases since a population is already infected. Molecular diagnostic methods that identify strain differences might be able to distinguish between infections from within the population and those entering from the

outside. However, reintroduction of disease from infectious individuals (e.g. animals with mastitis, footrot, bovine virus diarrhea (BVD), infectious bovine rhinotracheitis [IBR]) is one strategy that presents itself as persistence. In this case, there is a continuum of introductions (or reactivations) with a metapopulation structure<sup>22</sup> of, for example, populations of connecting farms. Figure 1 presents data from a recent study (BBSRC funded) tracking seroconversion to BVD of many cattle on one farm between years 1 and 2 of a cohort study, indicating a within-farm mini-epidemic that may have occurred through introduction of an infectious bovine from another farm, or from a bovine already present on the same farm. When the mechanisms for persistence equal the mechanism for successful introduction, then diseases may be controlled by managing these successful introduction mechanisms. This often turns out to be challenging enough; results from many years of study on measles in man (an equivalent disease to rinderpest in cattle) certainly testify to this.<sup>23</sup> However, we will argue that most persistent diseases utilize further routes that lead to a protracted infectious period, so that the pathogen truly persists to infect new susceptibles. Understanding the mechanisms for persistence is vital for understanding of endemic disease management.

### Persistence

Infectious endemic diseases are defined epidemiologically as those existing in a population with an Effective Reproduction Number ( $R_e$ ) of approximately 1; that is, on average every infectious individual infects



**Figure 1.** Evidence of seroconversion to BVD of cattle from one farm between years 1 (first visit) and 2 (second visit). Seroconverting animals are shown inside oval. The right panel compares serum samples from years 2 and 3 (third visit) where most cattle were seropositive for both years. Endemicity could be maintained by repeated introductions of infections, or could result from small outbreaks due to recurring infections from within the herd.

one susceptible individual over its entire infectious period,<sup>10</sup> and so the disease persists. When a disease enters a fully susceptible population, the mechanism for spread that creates an epidemic is characterized by the first-generation transmission of infection. Typically, this will be by infectious individuals successfully transmitting infection to susceptible individuals in the population. The size of this first generation of new infections has been referred to as the Basic Reproduction Number, or  $R_0$ . If the infection results in development of immunity, the population then shows an increase in the number of resistant individuals, the pool of susceptibles falls to below a threshold level and, without introduction of new susceptible individuals, the pathogen dies out. The effective R becomes less than 1 while the infection fades out. Currently, we see relatively few infections that behave like this. Fade-out means these infections are unlikely to become endemic diseases, and that these diseases are the “easier” ones to eliminate. Likely, we have already managed these infections through elimination.

The effort to remove endemic diseases appears to be far greater than the theoretical threshold for elimination based on introduction mechanisms.<sup>20</sup> This is because the introduction or invasion of a pathogen is not usually the only mechanism by which it persists in a population. Understanding persistence of pathogens is key to being able to assess whether elimination of a disease is possible. If elimination is not possible, then the pathogen-specific mechanisms for persistence can direct disease management programs (control programs).

### Factors Related to Persistence of Infection

Recent studies have shed more light on the distinction in dynamics between endemic infectious diseases and the (repeated) entry of previously eliminated infections. Endemic infectious disease may show additional complexities that are not captured in the conventional  $R_0$  components.<sup>33,34</sup> Although we need to know the specifics of persistence for each endemic disease that we wish to control, there are certain generic routes of persistence that we can consider. These generic complexities include host factors related to persistence, pathogen factors related to persistence and environmental persistence.

#### 1. Host factors related to persistence

##### *Complex pathogenesis*

The presence of a very complex pathogenesis with, for example, multiple infectious states including carrier states, intermittent shedding, seronegative carriers and reactivation. Complex pathogenesis is often not fully captured in mathematical models. Hence, the real ef-

forts needed to eliminate infection are not well predicted using mathematical models, and the resulting  $R_0$  estimates from these models are underestimating the true transmission potential. An example would be the complex pathogenesis of IBR, where both reactivation in immune animals and seronegative shedders appear to be present and constitute a challenge to elimination of infection.<sup>19</sup>

##### *Host heterogeneity in response to infection*

All hosts are not equal, and pathogens manipulate this host heterogeneity of genetic make up, age and sex differences to aid persistence. We have known for a long time that in macro-parasitic infections not all hosts are equal, some hosts are heavily infested and, if treated, the same individuals become heavily infested again.<sup>15</sup> We can postulate from the above that for some micro-parasitic infections this mechanism is also likely. We know, for example, with Johnes's disease (JD) that most of the shedding may come from a few “super shedders” in a herd.<sup>29</sup> Similarly, the persistently infected bovine in BVD disease is the key source of infection to the herd.<sup>42</sup>

Pathogens can extend their infectious period by altering a host's immune response to infection. We see this in BVD, where persistent infection occurs in individuals infected *in utero* before 120 days' gestation, when the pathogen is not recognized as foreign to the host. These persistently infected (PI) cattle are infectious “for life”, compared with cattle infected after birth which are usually infectious for just a few days. Several models of BVD persistence indicate it is these PI cattle that prevent fade-out of BVD from a herd. These PI animals also contribute to introduction of BVD in previously naïve herds. Some pathogens persist by partially evading the host immune system, e.g. tuberculosis (TB), or paratuberculosis. So, apparently healthy but infectious individuals lead to persistence of the pathogen. These individuals are also able to transmit infection between herds. This mechanism also affects detection of infected individuals, since immune based diagnostic tests may fail to detect infected individuals.<sup>41</sup>

Another heterogeneity in host immune response that eases endemicity of infectious disease is immunity that wanes over time.<sup>13</sup> Gradual loss of immunity over time, resulting in a continuum of models between the stable homogenous states of SIR and SIS (susceptible-infectious-susceptible),<sup>17</sup> is particularly observed in bacterial infections where either vaccination or natural infection results only in a short duration of immunity. An example of this is *Staphylococcus aureus* mastitis, where even a full natural infection does not lead to long-term protection.<sup>48</sup> With some infections, a prior infection may even lead to an increased risk of subsequent re-infection.<sup>47</sup> Such an increased risk obviously contributes to persistence in the population and is also respon-

sible for “backward bifurcation” (see below), leading to increased difficulty in eliminating the infection from a population.<sup>35</sup>

#### Host population density

Host population density influences persistence, with larger host densities resulting in higher likelihood of persistence. One reason stamping-out policies in the past were successful for elimination of some infectious diseases was that herd sizes were small. This may still be observed in countries and areas where such small herds dominate. For example, BVD has been eliminated from Norway where the average herd size is small.<sup>39</sup> An increase in herd size increases the risk of persistence in endemic diseases. Several mechanisms may be held responsible for this. First, in a larger herd a continuous supply of susceptible animals becomes available through birth. Second, larger herds have a lower probability of infection fade-out because of stochastic variability in the number of infectious individuals. Finally, in larger herds the number of new infectious introductions per unit of time may be larger.

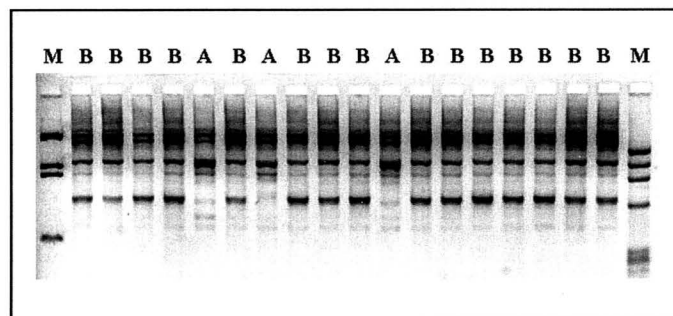
### 2. Pathogen factors related to persistence

Historically we have cultured bacteria and classified them by phenotypic and biochemical tests, which assumes vertical inheritance of genetic material to be the most important trait that classifies a bacteria. However, horizontal gene transfer occurs in all bacteria and the introduction of a new gene, e.g. via a plasmid, may change a bacteria from a non-pathogenic to a pathogenic state. In addition, mutations occur at each replication of a bacterium and these also create pathogen heterogeneity. Recent advances in molecular techniques<sup>37,50</sup> highlight that within a single species of a pathogen, strain variation occurs and strains vary in their behavior in hosts and in populations. Strain variability may lead to heterogeneity in parasite transmission and may give rise to strain competition and multiple parallel dynamics.<sup>21</sup> For example, some strains of *S. aureus*, *Streptococcus uberis* and *Escherichia coli* are apparently more udder-adapted than others.<sup>11,37</sup> These differences mean that in herds where udder-to-udder transmission dominates that the udder adapted strains dominate, but in a system where non-udder transmission dominates the less adapted strains will dominate. Figure 2 presents the result of strain typing in a herd where two pre-dominant strains caused most cases of *S. uberis* mastitis.<sup>49</sup> If strain heterogeneity is ignored, the estimated  $R_0$  is the weighted average of the individual  $R_0$  values of the different strains. However, a successful elimination will need to be based on the highest of the  $R_0$  values. Hence, strain heterogeneity tends to increase the likelihood of persistence.

### 3. Environmental factors related to persistence

The environment is a mechanism for persistence for some pathogens. The ability of pathogens to persist outside the host varies. To be of importance for persistence, the pathogens must survive longer than the period of infectiousness in the host. For example, it has been shown that *M. avium* subspecies *paratuberculosis* (MAP) can survive up to a year in the environment.<sup>45</sup> In this way, pathogens can persist for a limited period of time in the absence of susceptible individuals. This behavior has been overlooked for many diseases, and our reliance on culture (see above) may have led us to under rate the importance of the environment, since many pathogens may be viable but non-culturable outside the host.<sup>7</sup> Presence of environmental persistence of an infectious organism for a period of, say, 12 months (i.e. MAP<sup>44,46</sup>) indicates that the population processes that reduce the  $R_0$  to a value below 1 will need to be maintained for at least 12 months. Also, stochastic fade-out will be present in a much lower frequency with the presence of an environmental reservoir.

Pathogens may also remain endemic in a location for longer periods through infecting more than one host species. This increases the probability of successful persistence in each host species, since all mechanisms for persistence within each host species can be used in each species. If infection of multiple host species is an adaptation for persistence, then transmission between host species must occur. An example would be the persistence of TB, where a species other than cattle (badger) becomes infected and contributes to maintenance of infection in cattle.<sup>8,32</sup>



**Figure 2.** Example of random amplified polymorphic DNA (RAPD) PCR: *Streptococcus uberis* isolates from a bovine dairy herd collected during an outbreak of mastitis. Two strains (A and B) were identified among samples from 10 cows. M = molecular marker. These data are indicative of simultaneous outbreak dynamics of two (competing) strains.

## Mathematical Modeling

Mathematical modeling of infectious diseases has resulted in a greater understanding of dynamics of these infections within hosts, within herds and within regions or countries.<sup>2,28</sup> Particularly, introduction of the concept of reproduction ratio has contributed to our understanding of infectious disease transmission. The Basic Reproduction Ratio, also known as  $R_0$ , is defined as the number of secondary infections resulting from an infectious individual during its complete infectious period in a fully susceptible population. This parameter has a threshold phenomenon,<sup>9,10</sup> where values below the threshold of 1 result in the eventual die-out of infection and values above the threshold of 1 lead to smaller or larger outbreaks. The basic reproduction ratio is often calculated using data representing entry of the infection into a fully susceptible population,<sup>18</sup> although it may also be calculated using steady state data of infections.<sup>27</sup> Endemic infectious diseases are defined as those which exist in a population with a reproduction ratio of approximately 1; that is, every infectious individual infects approximately one susceptible individual over its infectious period. Note that this is the  $R$ -value of which the  $R_0$  is a special case (at time point zero, when all individuals in a population are still susceptible).

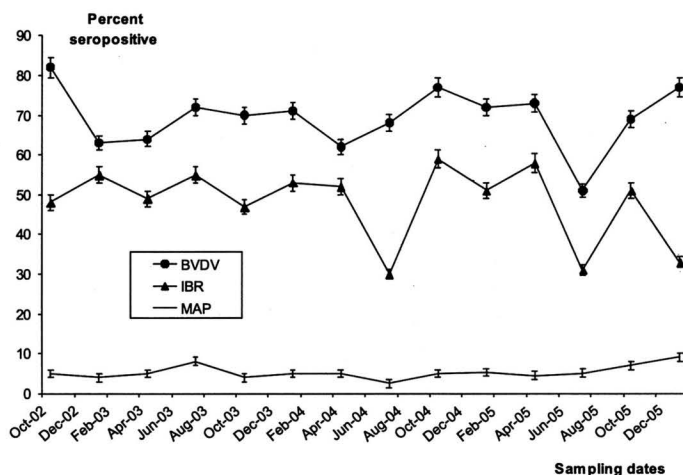
The  $R_0$  value of an infectious disease is used as a summary parameter for its ability to spread and maintain itself in a population. For example, in a simple SIR (susceptible-infectious-resistant) model the long-term, steady-state estimate of the percentage of susceptible individuals is estimated as  $1/R_0$ , and the prevalence of seropositives then as  $1-(1/R_0)$ . Figure 3 shows the seroprevalences of three endemic infectious diseases in England. These data are from a longitudinal study on 114 cattle farms. This then leads to use of  $R_0$  in the design of control programs. For example, assuming a perfect vaccine, the proportion of individuals to be minimally vaccinated at all times to control the spread of the infection is given by  $1-1/R_0$ .<sup>3</sup> More complex models then the simple SIR model can be designed and will result in different equations for these control parameters. However, the principle that  $R_0$  is used for the design of control programs remains. Since  $R_0$ , by definition, is capturing the dynamics of the infection when it enters a fully susceptible population, it may not necessarily reflect the full infection dynamics in an endemic situation.

Another example where mathematical models often fall short would be the modeling of very long infectious periods. Typically, mathematical models assume a negative exponential distribution in the duration of infectious period. However, with long infectious periods such as those observed with certain *salmonella* serotypes<sup>6</sup> and certain host-adapted *S. uberis* infections,<sup>49</sup>

this distribution is incorrect<sup>43</sup> and will lead to an underestimation of the  $R_0$  value.

Presence of additional complexities that lead to infection persistence often results in a much greater effort needed to eliminate infections than would be expected from the estimated  $R_0$  value of the infection. Presence of different mechanisms for entry of the infection into a susceptible population and for endemic persistence in a population (i.e. generation of super shedders by previous super shedders, increased susceptibility after initial infection, intermittent shedding, environmental survival), results in the concept of "backward bifurcation".<sup>12,40</sup> Essentially, this backward bifurcation is present when the  $R_0$  value of an infection increases when the infection becomes endemic in the population. Again, this results in increased efforts toward elimination of these endemic infectious diseases, as would be predicted from the  $R_0$  value. There is currently mostly theoretical evidence of this phenomenon. Presence of this backward bifurcation would result in situations where the classical or "naïve"  $R_0$  value may be reduced through infection control practices to a value less than 1, while disease persists. This backward bifurcation is shown in Figure 4, where disease persistence is present when the "naïve"  $R_0$  is less than 1 (Figure 4). Only when management practices are introduced that further reduce transmission (and thereby lower the "naïve"  $R_0$  to a value below a next threshold) does elimination occur.

Overall  $R_0$  is often a weighted average of all individual strains of an organism, all routes of persistence and transmission. Elimination is by definition removal



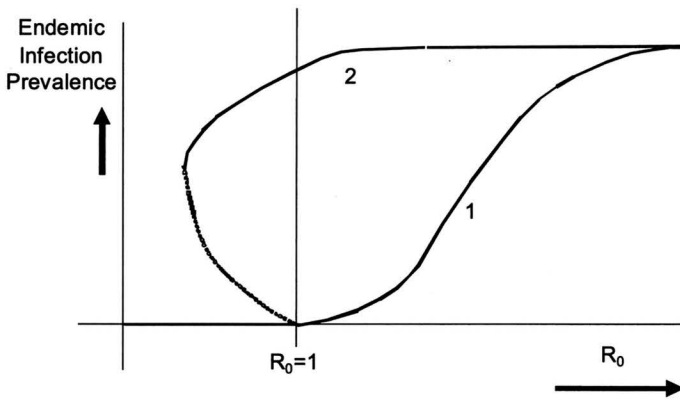
**Figure 3.** Prevalence of three endemic infectious diseases in England. Data shown are the seroprevalences from December 2002 until March 2006 of bovine virus diarrhea virus, *Mycobacterium paratuberculosis* (Johne's disease) and infectious bovine rhinotracheitis in 114 cattle herds in England (Unpublished data, University of Warwick Ecology and Epidemiology research group).

of all strains, and consequently developing control programs based on an average  $R_0$  may not lead to elimination. There will be sections of the host population (perhaps due to management or environmental circumstances) within which  $R_0$  will be greater than the average, e.g. young stock or animals housed in poorly ventilated barns. Alternatively as discussed above,  $R_0$  may not fully reflect the dynamics of infection maintenance in an endemic situation. If a model of an infectious process omits one (or more) routes of persistence, then elimination may be predicted but not achieved in reality. Practically, we need to know all possible routes

for persistence. This is difficult when endemic disease appears constant, and either cohort studies or perturbation to a system may be required to observe all possible routes for persistence. A theoretical model may be useful to assess the sensitivity of a system to a theoretical mode of persistence. This is the key issue to consider when developing control programs and when addressing apparent failure of control programs.

### Control vs. Elimination

Several arguments play a role when deciding whether an endemic infection should be eliminated or controlled. Arguments that need consideration are summarized in Table 1. Clearly, knowledge of the infectious disease and infection control technology are needed to eliminate an infection. Things to consider here would be diagnostic tests, diagnostic capacity and adequate information on pathogenesis. However, other factors such as animal demographics, economics, ethical and social issues play an important role here. The point is, this is not just an infection technical issue (which is mostly what we discuss in this paper), but other societal factors play a big role in the eventual decision to try and eliminate an infection from a population.



**Figure 4.** The concept of backward bifurcation. The horizontal axis represents increasing values of the  $R_0$ , and the vertical axis represents the endemically stable prevalence of infected individuals. Line 1 represents the classic relationship between  $R_0$  and the proportion infected (known as forward bifurcation). Line 2 represents the situation where an infection can maintain itself for a range of values for  $R_0$  below 1.

#### Disease control programs

The aim of a control program is to minimize disease and introduce permanent economically feasible and societal acceptable management changes that keep disease minimized. We can control a disease by altering the balance of susceptible, infected or immune individuals in a population. Culling and treating individuals leads to a large proportion of the population being susceptible (e.g. BVDV PI elimination reduces circulating

**Table 1.** Factors to consider when deciding on elimination versus control of endemic infectious disease agents.

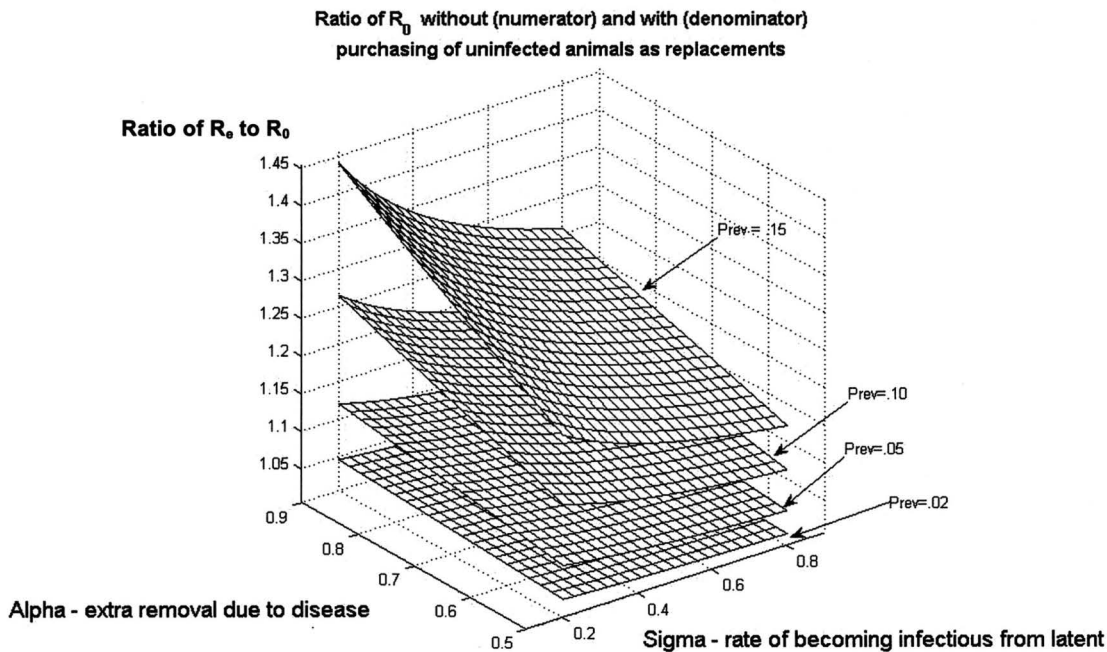
- Are the knowledge and technologies available to eliminate the infection:
  - adequate diagnostics
  - adequate molecular strain differentiation techniques
  - adequate information on pathogenesis
  - adequate mathematical models of infection dynamics
- A change in animal demography may complicate elimination:
  - large herd sizes
  - close proximity of wildlife species and livestock farming
- Economic considerations:
  - is it worthwhile to eliminate?
  - is it feasible to implement a realistic monitoring and infection response scheme once the infection is eliminated?
- Tools may be present that allow endemic presence without high economic costs:
  - vaccination
  - treatment
- Environmental, ethical and social considerations for elimination:
  - does elimination include controversial actions such as culling of wildlife?
  - is culling of infected animals accepted in society?

virus and increases susceptibility), and great care is required to reduce exposure of these susceptibles to infectious individuals. However, given it is clinical disease that affects health and well being of animals, infected-but-not-diseased individuals may in some cases be protected from disease. This is the basis of control with endemic stability, where host and pathogen coexist with minimal disease.<sup>30</sup> The ideal option would be to control through induction of long-lasting immunity at low risk and low cost, typically through vaccination.<sup>38</sup>

As a consequence of persistence and novel mechanisms for persistence, elimination and control of endemic diseases is more complex than we may have considered using naïve  $R_0$  estimates. This may explain apparent failures of control programs or explain why a new control program is unsuccessful or less successful than predicted. Where control is implemented the disease dynamics will change as a consequence of implementation, and control programs also therefore need to be reviewed and modified. For example, the practice of culling of infected livestock may affect endemic disease prevalence on a farm. When the national disease prevalence is equal to or higher than that on a given farm, then purchasing stock to replace culled infectious animals is not an option in an attempt for disease elimination. Consequently in a closed herd, culling of infected individuals leads to lower culling of other, potentially latent

infected, animals. This results in a relative longer survival of these latent infected animals and an increase in the rate of development of new shedders. Consequently, the  $R_0$  estimate would become higher, resulting in an increased effort necessary to eliminate infection. We illustrate this with the results of a simple MAP model in Figure 5. MAP is modeled here with a susceptible, latent and infectious state. Control exists of a test-and-cull program, where the test-positive (diseased) animals are culled with rate  $\alpha$ . Increasing this cull rate ( $\alpha$ ), when no susceptible replacement can be purchased, leads to a lower culling from all other classes, and therefore to an increase of newly infectious individuals. The ratio of  $R_0$  to  $R_0$  in the situation with and without purchase of certified susceptible individuals from outside is depicted in Figure 5. An increase in endemic disease prevalence, an increase in duration of the latent period and an increase in culling of diseased animals resulted in a larger  $R_0$  value. Figure 5 shows values up to ~1.5 times as large as in the situation where culled animals can be replaced by susceptible animals from outside the herd.

Another example where the control program itself may affect infection dynamics is bovine mastitis. In the 1950s, over 80% of mastitis in GB was caused by *S. agalactiae*. A control program to reduce mastitis caused by *S. agalactiae* was highly successful, and clinical cases



**Figure 5.** Ratio of  $R_0$  to  $R_0$  as it is impacted by purchasing from an endemically infected population, versus reducing culling for other (non-Johne's disease) reasons when the purchasing herd has a prevalence of Johne's disease of 0.15, 0.1, 0.05 and 0.02. The model has a susceptible, latent and infectious class. Sigma is the rate of movement from latent to infectious, and alpha is the extra removal due to clinical disease in the infectious cows.

went from over 120 per 100 cows per year to less than 80 per 100 cows per year. However, whilst the amount of mastitis attributable to *S. agalactiae* decreased, the amount of clinical mastitis overall did not plummet by the expected 80%. *S. aureus* and other streptococcal spp became more dominant. In the 1960s, a second control program was proposed known as the five-point plan. Once again this was very successful, reducing clinical cases to about 40 cases per 100 cows per year. However, from the early 1980s onwards there was no further reduction in clinical mastitis; recent data suggest the incidence is currently nearer to 50 cases per 100 cows per year and the dominant pathogens are *E. coli* and *S. uberis*. The control program has changed the major source of infection from other cattle and contagious type pathogens to the environment and environmental pathogens.

### Discussion and Conclusions

Invariably, there will be a discussion on elimination of endemic infectious disease when these infections cause substantial economic or societal losses. A good example of this would be the potential elimination of bovine TB, BVDV or MAP.<sup>4,16,25</sup> We argue that elimination of endemic infectious diseases is more complex than the estimates from known  $R_0$  values would suggest. Endemicity in itself may be associated with additional mechanisms than those that give rise to the initial establishment of infection in a fully susceptible population. Examples of these additional mechanisms include (micro) parasite heterogeneity, environmental survival (either with or without additional secondary host dynamics), or host heterogeneity. Examples of the latter include development of highly infectious states that is partly determined by prevalence of the infection itself (for example, super-shedders<sup>26</sup>), or heterogeneity in susceptibility and immunity. This leads us to conclude that control of endemic infections is more complex and elaborate than control of epidemics in previously eliminated infections.

Elimination of previously endemic infections also implies development and maintenance of an adequate monitoring system and the presence of an epidemic control program if a new introduction occurs. Hence, discussions on elimination should not only include the efforts and costs of elimination of endemic infections, but also the future expenses and consequences of monitoring and outbreak control. For countries or regions these future expenses and consequences may be acceptable, but may be prohibitive for individual farmers considering elimination of a current endemic infection in their herd. Elimination of MAP may be a good example; control procedures aimed at reducing costs of clinical cases on a farm would include Good Management Practices (GMPs) such as hygienic procedures in calving

stalls, reduction of contacts between adult animals and young stock, rational testing procedures and limited culling of shedders. In contrast, elimination would require the above mentioned procedures in addition to aggressive testing and culling over a long period (multiple years). If elimination has been successful, intensive testing remains necessary and a return to aggressive test-and-cull programs is called for when reintroduction of infection occurs. In such cases, infection control may be a much more economically attractive alternative to elimination.

Endemic diseases are complex. Advances in understanding host and pathogen heterogeneities have increased our epidemiological understanding of additional complexity of these diseases, and may help in the design of appropriate control strategies. When considering control of endemic diseases, the infection processes themselves as well as the influences of host, pathogen and environment, societal influences, and attitudes to disease control through economic, legislative and social drivers should be taken into consideration. Multidisciplinary research with epidemiologists, ethologists, molecular biologists, population biologists, veterinarians, geneticists, economists, political scientists, statisticians, mathematicians and social scientists may help to address how some of these externalities influence control of endemic diseases. For each endemic disease considered for control or elimination, a detailed knowledge of the infection process and mechanisms for persistence is essential. Control programs must address mechanisms of introduction of a disease, and include control procedures for routes of persistence. Control programs need to be continuously re-evaluated, since the disease processes may change due to the implemented control measures. We can improve animal health now if we use all the knowledge at our disposal and in the future if we target research questions at understanding persistence.

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