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Cover photo: Bison graze outside the Roosevelt Arch at the park's north entrance. (NPS)

Vaccination Strategies for Managing Brucellosis in Yellowstone Bison

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INTRODUCTION

Concerns over the risk of bison from Yellowstone National Park transmitting brucellosis to cattle herds adjacent to the park led to the development of an Interagency Bison Management Plan. The objective of this plan is to maintain a wild, free-ranging population of bison and to address the risk of brucellosis transmission to protect the economic interests and viability of the livestock industry in the state of Montana (National Park Service 2000). The plan identified bison vaccination as a potential method for managing brucellosis transmission risk, and the National Park Service is now proposing to implement a remote vaccination program aimed at reducing brucellosis infection in bison. The Service is responsible for completing an Environmental Impact Statement to assess the effectiveness of remotely vaccinating bison. The complexity of implementing a brucellosis vaccination program requires the assessment of specific vaccination strategies. An effective vaccination program will use current understanding of brucellosis epidemiology to develop an efficient management strategy. We developed an individual-based model to evaluate alternate vaccination methods aimed at reducing brucellosis infection in Yellowstone bison and predict how brucellosis infection might respond under each management approach.

Brucellosis was discovered in Yellowstone's bison population in the early part of the 20th century. Though the disease is not a threat to the long-term survival of the Yellowstone bison herd, concern that bison may transmit brucellosis to cattle on neighboring lands has been an issue for several decades (Plumb and Aune 2002). As a result, bison are subjected to hazing and culling operations as they attempt to migrate outside the park. Conflicts between state and federal agencies, and public concern over the treatment of bison, demonstrated the need for a comprehensive bison management plan.

Models can be useful decision-making tools for evaluating management strategies when it is necessary to proceed despite uncertainty (Gross and Miller 2001). Much remains to be learned about brucellosis dynamics in Yellowstone bison. Modeling our understanding of brucellosis epidemiology and appropriate vaccine control strategies is a necessary step for the development of a bison vaccination program. The purpose of this modeling effort was to provide decision makers in Yellowstone with a tool for predicting how brucellosis seroprevalence in bison might respond under proposed management alternatives. The following literature review synthesizes our understanding of brucellosis in bison and aided in constructing model processes and estimating model parameters.

The Disease Brucellosis

Brucellosis in Yellowstone bison is caused by *Brucella abortus*, a bacterial organism transmitted by ingesting infected birth products or infected milk. Brucellosis is not native to North America and was likely introduced to Yellowstone bison by European cattle (Cheville et al. 1998, Nicoletti 2002). The disease was first detected in Yellowstone's bison herd in 1917 (Mohler 1917) and is not considered a major factor regulating population growth (Dobson and Meagher 1996), though recent analyses suggest this assumption may be suspect (Fuller et al. 2007*a*, *b*).

Brucella abortus usually localizes in the organs and tissues of the reproductive system prior to being shed in the environment during an infectious event. For this modeling effort, we defined an infectious event as the shedding of *B. abortus* during an

abortion or in the placenta and fluids of a live birth. These are the only two known routes of horizontal transmission involving *B. abortus* infecting herd members within bison. Though there may be differences in the amount of *Brucella* shed during these two types of events, we assumed that the volume of infectious material was substantial enough to treat the two events equally with regard to transmission (S. C. Olsen, Animal and Plant Health Inspection Service, personal communication). The conditions influencing the proportion of either of these events is unknown, but believed to be directly related to the maintenance of *B. abortus* in the bison population. The objective of bison vaccination is to stimulate an acquired immune response to *B. abortus* that reduces the potential for infection and transmission. Effectively modeling such an approach requires integrating the biology of the host and pathogen and the epidemiology of brucellosis within the bison population.

Brucella Pathogenesis

Understanding the pathogenesis of *B. abortus* in Yellowstone bison, including the cellular events, reactions, and mechanisms occurring in the development of disease, is important for comprehending the epidemiology of brucellosis. The evolutionary success of *B. abortus* lies in its adaptive ability to hide from the host's defense system. Brucellae are facultative intracellular pathogens, which evade the host's immune system by replicating within the host's white blood cells (Dornand et al. 2002). This phenomenon of intracellular persistence has long been suggested as an explanation for the chronicity of brucellosis, as well as relapses following treatment (Braude 1951*a*, *b*; Spink 1952). The intracellular environment sustains extensive replication, allowing bacterial expansion and the subsequent transmission to new host cells, frequently achieved through the heavily infected aborted fetus (Grovel and Moreno 2002).

The complex processes associated with *B. abortus* infection and transmission are linked to the strategy of the pathogen. *Brucella* organisms are pathogens whose ultimate goal is to propagate in their preferred niche, the cell (Grovel and Moreno 2002). Once a bison consumes *Brucella*, white blood cells (macrophages) from the bison's immune system engulf the bacteria. *Brucella* species have developed the ability to avoid destruction by limiting fusion with the host cell's endosome-lysosome pathway (Kohler et al. 2003). This avoidance strategy permits *B. abortus* to survive within specific white blood cells of the host while providing protection from the host's humoral and bactericidal defense mechanisms. Macrophages invaded by pathogenic bacteria can sometimes induce their own death (apoptosis) to prevent bacterial invasion of other macrophages (Weinrauch and Zychlinsky 1999). *Brucella* has the ability to inhibit apoptosis and protect the infected host cell, thereby maintaining infection (Dornand et al. 2002). Intracellular protection and replication are crucial components of incubation, latency, and chronic infection of Yellowstone bison (Nicoletti and Gilsdorf 1997).

Incubation

Incubation, the time between the entry of the pathogen in the host and first expression of infection, is a key component influencing the initiation of the infectious state. The *Brucella* incubation period in bison is variable and is affected by several factors such as gestation, exposure dose, age, vaccination, and unknown host-resistant influences (Nicoletti 1980). *Brucella* organisms preferentially replicate in placental cells during the middle and late stages of gestation. During this incubation period, these placental cells represent a second host cell type, and allow expansion of *Brucella* in the reproductive

tract; thereby playing a critical role in the pathobiology of *Brucella* infections (Anderson et al. 1986, Meador and Deyoe 1989). These placental cells are thus an important interface between the maternal and fetal circulation systems (Grovel and Moreno 2002, Roop et al. 2004) and serve as an incubation site of *B. abortus* prior to shedding during an infectious event.

Replication within these cells is enhanced in ruminants by the production of large quantities of erythritol, a natural sugar, in placental trophoblasts. Erythritol is the favored carbon source for *B. abortus* strains (Meyer 1967, Sperry and Robertson 1975) and it has been postulated that the ability of *Brucella* to metabolize erythritol plays a critical role in both the virulence and growth rate stimulation of this bacteria in the ruminant reproductive tract (Anderson et al. 1986, Roop et al. 2004). Additionally, the placenta of all ruminants, including cows, goats, and sheep, have been found to contain high concentrations of erythritol (Anderson et al. 1986).

The extensive replication in placental trophoblast cells causes a rupture compromising placental integrity by allowing the bacteria direct access to the fetus (Bellaire et al. 2003). The resulting abortions and premature calves are highly infectious due to a large number of *Brucella* on the fetus, placenta and birth fluids. Adequate incubation time is required for *B. abortus* to induce shedding of the bacteria in recently exposed, pregnant bison. **Therefore, we have included an incubation component in the model to determine if there has been adequate incubation time to induce an abortion in a pregnant, susceptible bison recently exposed.**

Latency

Latency refers to the quiescent state of the host during disease incubation. The latent state is directly related to *B. abortus'* ability to survive for prolonged periods at relatively low numbers within the bison host. After being ingested by white blood cells, the bacteria are transported to the tissues in the lymphoid system where they are able to persist. In late gestation *Brucella* may undergo quick growth when activated by pregnancy hormones, such as progesterone, when bison cows reach reproductive maturity (Cheville et al. 1998).

The pathogen's ability to persist undetected by the host immune system results in a class of individuals called latent carriers. The occurrence of latent carriers among cattle (heifer syndrome) is widely accepted (Van Den Bron and Vervoorn 1965, Plommet et al. 1973, Lapraik et al. 1975, Catlin and Sheehan 1986), and experimental evidence indicates that they occur in bison and elk (Thorne and Morton 1978, Olsen and Holland 2003). Latency associated with *B. abortus* is problematic for disease management because infected reproductively immature animals can test negative on serologic tests but shed *B. abortus* when reproductively mature. Experimental cattle studies have found that approximately 20% of calves born to infected mothers were latently infected (Plommet et al. 1973, Lapraik et al. 1975). A thorough epidemiological study conducted by (Wilesmith 1978) estimated that 2.5% of heifer calves born to serologically positive dams reacted in early adulthood and constituted a risk to newly established herds.

In cattle, few infected cows ever recover from infection, and should be considered carriers for life, even if no abortions occur (Ragan 2002). This is not generally a concern in domestic cattle herds because infected individuals are removed to prevent future risk of transmission. The identification of infected (seropositive) bison does not occur with such frequency and individuals may recrudesce. Recrudescence, the relapsing of quiescent animals to the infectious state near parturition, is a concern with Yellowstone

bison. The rates of bison recrudescence are not known, but are important for evaluation of disease dynamics (Williams et al.1997).

Pregnancy rates of Yellowstone bison are estimated to be 89% and, with this relatively high proportion of adult cows becoming pregnant annually, normal birth events that deposit an infected placenta onto the landscape contribute to the amount of *Brucella* that is shed. The causes of recrudescence and *Brucella*-shedding in the placenta of subsequent live births is uncertain, but is assumed to be related to an increase in stress (Cheville et al 1998). The combination of density-independent (climatic factors influencing annual variability) and density-dependent factors (resource limitation during periods of high energy needs) may be important drivers of recrudescence and chronic infection of Yellowstone bison. **For this modeling effort, we assume that bison never truly recover from brucellosis and that adult females can transiently shed *B. abortus* throughout their reproductive lives.** It is the combination of the disease's ability to persist undetected for long periods, latency, and then rapidly replicate during the favorable conditions of late pregnancy that leads to the state of chronic infection observed in Yellowstone bison.

Chronicity

A chronic disease is of long duration and can result from the prolongation of two components: 1) the period between initiation of the disease process and the onset of clinical disease (latency); and 2) the period between the onset of clinical disease and termination (Woebser 1994). The potential inability of bison to completely recover from infection of *B. abortus* is relevant to the latter component of chronic infection. Chronically infected female cattle have been observed to periodically and transiently become bacteremic and shed *B. abortus* in genital infections (Manthei et al 1950, Lambert et al. 1960). Experimental work has concluded that brucellosis in bison does not differ from what has been observed in other ruminants (Davis et al. 1990, Davis et al. 1995). Brucellosis in bison may be similar to chronically infected domestic cattle herds, with young animals aborting pregnancies more than older animals and only a small percentage of infected females aborting in any one calving season (Rhyan et al. 1994).

The intracellular hiding ability of *B. abortus* allows for low numbers of brucellae to persist within individual bison thus resulting in a chronicly infected population. Reactivation within some individuals during favorable conditions of late gestation explains why the number of infected females is always greater than the number that are shedding or bacteremic (Cheville et al. 1998). **By considering disease incubation periods and recognizing that individual cows may recrudesce and intermittently shed *Brucella* throughout their reproductive life, our model addresses the potential transient shedding of *B. abortus* caused by chronic infection in Yellowstone bison.**

Brucellosis Epidemiology

The epidemiology of brucellosis in bison and cattle is thought to be similar (Roffe et al. 1999) and most pregnant bison exposed to an infectious dose at the proper time will, like most pregnant cattle, abort their pregnancy (Davis et al. 1995). Chronically infected female cattle periodically shed *B. abortus* in birth tissues and these infectious events are detectable because livestock are contained within fenced pastures. Detecting infection and the shedding of *Brucella* within Yellowstone's free-ranging bison herd, however, is problematic. Identifying the state of infection within the bison population relies on

diagnostic tests that are essential for evaluating model simulations comparing different management strategies.

Brucellosis diagnostics

Brucellosis is diagnosed in bison through two types of tests: serologic tests and bacterial cultures. Serologic tests provide indirect evidence of infection because they detect antibodies (responses to infection), not living bacteria. Therefore, seronegative animals may actually be infected, if tested during the early stages of disease incubation, because serologic tests are not sensitive enough to detect low levels of antibodies in the early stages of infection (Cheville et al.1998). Additionally, large exposure doses can shorten both the incubation period for *B. abortus* and the time until clinical infection. Thus, antibodies will develop sooner and increase the effectiveness of the test (Deyoe 1980).

The fluorescent polarization assay (FPA) is the diagnostic test of choice for detecting brucellosis in bison because of its high sensitivity and specificity values and adaptability to field use (Gall et al. 2000, Gall and Neilsen 2001). Nielson and Gall (2001) used fluorescent polarization assays on serum from 91 culture-positive bison and obtained high levels of sensitivity (94.5%) and specificity (99.5%). Alternatively, bacterial cultures are better tests for identifying infected animals, but the ability of *B. abortus* to persist in small numbers in certain tissues complicates diagnosis. Brucellae grow very slowly and culture tests both take longer (sometimes weeks) to obtain results (Cheville et al.1998) and also require specific tissues that are most efficiently collected only from dead animals. Therefore, culture tests cannot be used during management captures when quick diagnoses are needed. However, culture tests can be used to estimate the reliability of serologic tests when both tests are done on the same animals. Indirect tests, such as serologic tests, may be the most efficient way to monitor the prevalence of chronic infectious disease in a population, but do not provide information on the specific disease states (infected vs. infectious) needed for epidemiological modeling. Although not a gold standard, culture tests are the best test currently available for identifying actively infected bison, and should be the basis of evaluation of all other diagnostic methods (Nicoletti 1980).

Roffe et al. (1999) investigated the relationship between serologic responses in Yellowstone bison and the ability to culture *B. abortus*. Their findings indicated that serologic tests are a much better predictor of infection than previously thought. Previous data on Yellowstone bison suggested there were both fundamental differences between bison and cattle, and serology tests were a poor indicator of *Brucella* infection; less than 20% of seropositive animals identified as infected (Meyer and Meagher 1995). Roffe et al. (1999) were able to culture *B. abortus* in almost half (46%) of seropositive female bison sampled, and concluded that serology data from chronically infected cattle herds could be applied to Yellowstone bison. Estimated brucellosis seroprevalence rates of Yellowstone bison are believed to fluctuate between 40-60% (Cheville 1998; Bison Ecology and Management Office 2005). **For this modeling effort, we estimated that 46% (taken from Roffe et al. 1999) of Yellowstone seropositive bison were culture positive animals and considered to be actively infectious. We assumed, based on the use of the fluorescent polarization assay as a diagnostic tool, that all actively infectious bison and a high proportion of latent infected animals could be diagnosed as positive under boundary capture scenarios.**

Horizontal Transmission

Host-pathogen models are essential for designing strategies for managing disease in wildlife, and transmission is the key process in a host-pathogen interaction (McCallum et al. 2001). The risk of brucellosis transmission is determined by the number of infectious events (*Brucella* induced abortions and infectious live births) that occur, the presence and survival of *B. abortus* in the shed tissues, and the exposure of a susceptible host (Cheville 1998). Transmission of *B. abortus* is generally comprised of the following two distinct events: 1) *B. abortus* is shed into the environment; and 2) susceptible individuals ingest the infectious material, initiating the process of infection. An exception to this is the case when an infected cow passes the disease on to her calf either transplacentally or through infected milk.

Of the two types of infectious events, abortions and live births, abortions may present a greater risk of *Brucella* being transmitted. Abortions usually occur during the third trimester of pregnancy (Cheville et al. 1998), which coincides with winter conditions increasing transmission probability by concentrating bison into tighter groups. Additionally, abortions disrupt hormonal control and cause the placenta to be retained. The retained placenta can attract other herd members and extend the exposure period in space and time (Cheville 1988). Early observers have reported retained placentas in bison on the National Bison Range (Creech 1930) and in Yellowstone (Rush 1932). More recently, Bevins et al. (1996) observed retained placentas for greater than 24 hours in aborting bison experimentally challenged with *B. abortus*. Placental retention has also been observed in Yellowstone bison following normal calving events (BEMO data) and therefore should not be viewed as an indicator of a *Brucella*-induced abortion. Observations of Yellowstone bison with retained placenta in months proceeding the calving period are infrequent.

Transmission of *B. abortus* in Yellowstone bison is believed to occur primarily through contact with an aborted fetus (Cheville 1998). Cumulatively, in select studies, 82% of 90 bison experimentally infected with *Brucella* strain 2308 aborted or had live, but nonviable, calves from which *B. abortus* was isolated (Williams et al. 1997). In a controlled study, nonvaccinated elk challenged with *B. abortus* strain 2308 aborted at a rate of 88% (Kreeger et al. 2002). Similarly, Olsen et al. (2003) found that 96% (26 of 27) of non-vaccinated bison challenged with field strain *Brucella* aborted their pregnancy. Bevins et al. (1996) observed abortions in 5 of 6 bison challenged with *B. abortus* during their second trimester of pregnancy. Abortions in elk populations were estimated to occur in 7% (Smith and Robbins 1994) and 12.5% (Herriges et al. 1991) of pregnancies. Despite this preponderance of support for *Brucella*-induced abortions, field observations of these events are rare. *Brucella*-induced abortions have been confirmed through the isolation of the bacteria from the aborted fetus of a free-ranging bison in Yellowstone (Rhyan et al. 1994), but such observations are infrequent in Yellowstone.

As an explanation of the infrequency of observed abortions in the Yellowstone bison herd, Meyer and Meagher (1997) hypothesized that exposure early in life, via transmission through infected milk, provides resistance to abortions in young bison cows. Early exposure of this type may provide protection against later abortions compared to experimental studies exposing naive animals (control animals in vaccination efficacy studies) in mid gestation (Olsen et al. 2003). In experimental studies, calves fed large

amounts of *B. abortus* in the first 15 days after birth acquired a degree of immunity against subsequent exposure (Nagy and Hignett 1967). Likewise, oral administration with attenuated *B. suis* has been used successfully in China (Xin 1986) for protection of livestock. The oral route for vaccine delivery has provided protection in experimentally immunized cattle with *B. abortus* Strain 19 (Nicoletti and Milward 1983).

In view of the apparent paucity of abortions, young bison must gain exposure to *B. abortus* from other sources (Meyer and Meagher 1997). In cattle, abortions are usually seen during the first pregnancy after infection, but the placenta can be infected in subsequent pregnancies where *B. abortus* is shed during delivery of normal calves (Timoney et al. 1988). Thus, live births are potentially infectious events and *B. abortus* has been cultured from vaginal swabs of cows following parturition and in tissues left at birth sites. In addition to *B. abortus* being shed during abortions and infectious births, another source of transmission may occur vertically between the infected cow and her calf.

Vertical Transmission

Brucella abortus is known to cause mammary gland infections (Bevins et al. 1996) and can be transmitted vertically, from cow to calf, through infected milk (Nicoletti and Gilsdorf 1997, Ragan 2002, Olsen et al. 2003). Excretion of *Brucella* in milk is intermittent and there is large variation in the number of bacteria that are shed (Brinely-Morgan and McDiarmid 1960). Though bacterial numbers in milk are lower than in an infected placenta, they are typically high enough to present a serious risk of transmission (Cheville 1998). Nicoletti and Muraschi (1966) found 52% of cattle with positive milk titers were also culture positive, and infected bison cows have been observed to excrete *B. abortus* in milk within three weeks of infection (Davis et al. 1990). Bison calves in Yellowstone nurse for 8-10 months (Meagher 1973). It has been speculated that a proportion of these calves orally receive an ongoing, low dose of *B. abortus* during this nursing period, thereby allowing them to develop resistance to abortion (Meyer and Meagher 1995). Seroprevalence data collected during boundary management operations suggests that approximately 50% of Yellowstone bison are exposed to *B. abortus* prior to reaching two years of age (Treanor et al. 2007).

The success of vertical transmission depends on host survival, reproduction (Ewald 1994), and the virulence of *B. abortus*, which is believed to be low in bison (Dobson and Meagher 1996). The role vertical transmission plays in the maintenance of *B. abortus* in Yellowstone bison is unclear, but may help explain the infrequency of observed abortions, high seroprevalence rates among young animals, and latent infection. *Brucella* was not cultured from the mammaries of a small sample of Yellowstone bison and was found in only a single milk sample of 40 radicollared Yellowstone bison that were diagnosed as seropositive (Rhyan 2000**). We addressed the potential of *B. abortus* being shed through infectious live births and vertical transmission to calves by incorporating these transmission sources into our modeling effort. We made the assumption that a proportion of latently infected adult cows will recrudesce in any given year and have an infectious live birth. Also, a proportion of calves born from these infectious births will become infected through vertical transmission.**

Exposure

Another key component of brucellosis transmission is the number of exposures that occur during an infectious event. This factor ultimately depends on the behavior of the

bison cow at the time of parturition. Bison tend to give birth in close proximity to other group members, which increases the likelihood of transmission. Interactions of herd members with the newborn calf, including licking and nudging, have been observed in Yellowstone bison (Aune et al. 1998). This oral route of transmission is believed to be the most important route of exposure.

The massive amount of bacteria that are shed during these events combined with the strong attractant effect of expelled fetal membranes are the two factors that drive transmission of *B. abortus* and ensure perpetuation of the disease (Cheville 1998). **Field abortions have rarely been observed, but live bison births are commonly observed. We used these observations to estimate the number of exposures per infectious event.**

Vaccination

Vaccination is the preferred method of reducing brucellosis seroprevalence in Yellowstone bison (National Park Service 2000). Strain RB51 (SRB51) is the official brucellosis vaccine for cattle in the United States and provides significant protection in cattle (Davis and Elzer 2002), but safety and efficacy of the vaccine in bison is not clear. The conflicting results of experimental studies indicate a further need for vaccine development. The effectiveness of a vaccination program depends on an efficient delivery of a safe and efficacious vaccine that can be identified for monitoring the program's success. Though not perfect, SRB51 appears to be a potential candidate.

Vaccine Safety

The safety of SRB51 has been addressed and experimental studies have presented conflicting results. Palmer et al. (1996) demonstrated that SRB51 has an affinity for placental tissues and can induce abortions in pregnant bison vaccinated after mid gestation. However, Davis and Elzer (1999) found multiple infections of SRB51 to be safe in pregnant bison with no abortions or isolations of SRB51 observed. An explanation for the disparity between these studies is that bison in a herd chronically infected with *B. abortus* may develop immunologic responses that prevent the adverse effects caused by SRB51 (Davis and Elzer 2002). The results of Olsen and Holland (2003) suggest that bison vaccinated with SRB51 during calf-hood may be safely booster-vaccinated during the first pregnancy, thereby making early gestation a potentially safer period for vaccinating adult pregnant bison. **For our modeling effort, we assumed that vaccination did not contribute to additional calf mortality through early termination of the pregnancy.**

Vaccine Efficacy

The efficacy of SRB51 is determined by protection from infection and abortion following challenge with a virulent strain (S2308) of *B. abortus*, and the amount of protection conveyed to bison from SRB51 vaccination is not precisely defined (Davis and Elzer 2002). Olsen et al. (2003) demonstrated that vaccination of bison calves offers protection against vertical transmission (i.e., intra-mammary and fetal infection) in non-aborting vaccinates, as well as protection from abortions and placental infection. Alternatively, Davis and Elzer (1999) concluded that SRB51 did not confer significant protection in vaccinated bison despite intensive (three injections) vaccination efforts. Thus, they concluded SRB51 was safe, but had little or no efficacy in adult bison. Also, they suggested the efficacy of SRB51 had not been determined in a statistically

significant number of vaccinated bison calves (Davis and Elzer 2002). These discrepancies between the two studies demonstrate there is uncertainty in the level of protection offered by SRB51.

Despite conflicting experimental results over safety and efficacy, SRB51 can be used monitor vaccination status in free-ranging bison. Bison vaccinated with SRB51 remain seronegative at all times when tested with standard serologic tests, though antibody responses to SRB51 can be detected by using a dot-blot assay (Olsen et al. 1998). This enables distinguishing between seropositive and seronegative animals captured during management operations, as well as for identifying the proportion of vaccinates in the population.

Vaccine Delivery

Delivery proposes a problem when trying to vaccinate wildlife and, currently, the most feasible method of remote vaccine delivery to Yellowstone bison is through use of biodegradable projectiles ("biobullets"). Ballistic vaccination has been used to inoculate free-ranging elk on feedgrounds in Wyoming (Herriges et al. 1989) and has been tested experimentally with bison. Olsen et al. (2002) identified that ballistic inoculation of bison with SRB51 induced an antibody response, but failed to induce a significant cell-mediated immune response in comparison to hand injection of the vaccine (parenteral vaccination). The study used biobullets containing a compressed SRB51 pellet. Vaccine packaging using photopolymerized poly(ethylene glycol)-based hydrogels as a payload vehicle rather than compressing the vaccine demonstrated immunologic responses similar to parenteral vaccination (Olsen et al. 2006). **This research suggests that remote vaccination of bison in Yellowstone has the potential to offer vaccine protection at the same level as hand injections given at boundary capture facilities. Thus, we assumed both vaccine delivery methods offered the same level of protection.**

Duration of Protection

The duration of protection provided by a single SRB51 dose is unknown, but older cows may need to be booster vaccinated to extend the protection of the vaccine given during non-reproducing years (Olsen and Holland 2003). SRB51 can be packaged into biodegradable bullets and delivered to Yellowstone bison with an expected high degree of success (R. Wallen, National Park Service, unpublished data). Biobullets are packaged with live vaccine under controlled laboratory conditions, which reduces human safety concerns. Field crews do not need to handle liquid vaccine and the potential for leaving a delivery vessel in the field is eliminated. Also, ballistic delivery allows for the dosage control needed for adult bison that are more susceptible to vaccine-induced abortion and, therefore, require a lower volume of vaccine than reproductively immature individuals (Palmer et al. 1996, 1997).

Previous modeling efforts

Four modeling efforts have been conducted to better understand brucellosis dynamics in the Greater Yellowstone Area. The focus of these models varied from a single species, bison, to multiple species, bison and elk. Modeling approaches differed as well, and ranged from deterministic models to stochastic, individual-based methods.

Peterson et al. (1991) used an age-structured simulation model to evaluate *a priori* the effects of various management actions proposed for addressing brucellosis in Grand

Teton National Park. The simulation model was used to assess three bison-brucellosis management strategies: 1) female calf vaccination only; 2) vaccinating females of all ages; and 3) test, removal, and vaccination situations. The model was developed in three phases: 1) representing the population dynamics of a brucellosis-free herd; 2) identifying the influence of *Brucella* on herd population dynamics; and 3) assessing the effects immunization might have on the disease. A goal of reducing seroprevalence below 10% was used to compare success of the proposed strategies. The model simulated vaccination of two groups (female calves only and all females) at different levels of vaccine efficacy.

Model results suggested a highly effective vaccine (90% efficacy) is required to reduce seroprevalence below the desired 10% level by vaccinating 95% of either calves alone or all female bison. Alternatively, the testing and removal of seropositives, while vaccinating either female calves or females of all ages, reduced the percentage of seropositive females much faster than vaccination alone. Model assumptions included a fixed brucellosis transmission rate and simulations suggested that *B. abortus* transmission would have to be decreased considerably (< 5%) to reduce the percentage of seropostitive animals to less than 10% of the herd.

Dobson and Meagher (1996) used a deterministic model to address epidemiology of brucellosis in the Greater Yellowstone ecosystem. The model was created using the susceptible-infected-recovered (SIR) framework for infectious disease (Anderson and May 1991). Within this framework, the host population was divided into susceptible, infected, and resistant disease classes. Infected individuals were assumed to maintain the infection for 1-2 years, after which they recovered and entered a resistant or immune class of host. These types of analytical models are beneficial because of their ability to identify threshold values of disease establishment. The model used population and seroprevalence data to identify the threshold values for brucellosis establishment based on infected herds in Yellowstone and other national parks in the United States and Canada. The authors concluded that 200-300 animals were necessary for sustained infections, with seroprevalence rising as the population exceeded this threshold. Simulations suggested that once a herd dropped below this number, brucellosis was not present.

Elk are an additional carrier of brucellosis and complicate brucellosis risk management in the Greater Yellowstone Area. Dobson and Meagher (1996) used a two-species brucellosis model that included both bison and elk as hosts. Rates of transmission between elk and bison were determined by the amount of range overlap and the tendency of the two species to aggregate together while foraging. Because of the substantially lower level of brucellosis infection in elk, it was assumed *Brucella* could not sustain itself in elk without transmission from bison.

The dynamics of the model were most sensitive to the population density at which the herd equilibrated, the transmission rate, and the pathological impact of *B. abortus* on host fecundity and mortality. It was assumed that the bison herd would equilibrate at 4500 and elk at 25,000. Parameter values for density-dependent host birth reductions were derived from these assumptions. Transmission was represented by a simple mass action term (i.e., every individual in the population was equally likely to contract the disease). Vertical transmission, disease passed from mother to offspring, was incorporated into the model with a high proportion (90%) of infected females producing infected calves.

Because the authors felt the population was growing close to its maximal rate, the model used small parameter values for the influence brucellosis had on mortality and fecundity.

The analysis suggests it would require near eradication of the bison population to produce a significant reduction in disease prevalence. Also, there would be no guarantee that brucellosis would not re-establish unless the bison population was kept at low levels. Alternatively, an effective vaccination program would require over 50% of the population to be inoculated based on the model's estimate of the reproductive rate of *B. abortus*.

Gross et al. 1998 constructed a stochastic, individual-based model to investigate the dynamics of brucellosis infection in the Greater Yellowstone Area. The model tracked each individual in the population, and monitored births, deaths, abortions, and infection status through time. Both yearly and weekly time steps were used. Population processes occurred annually, while reproduction- and disease-related components were modeled weekly.

The individual-based approach was used because it allowed for a more detailed representation of transmission than the susceptible-infected-recovered (SIR) modeling framework. The model included a detailed sub-model for pregnant cows that addressed the role of *Brucella* incubation in host animals infected during pregnancy. The model also incorporated the probability of a cow having an infectious births and the probability of the cow remaining infected. An equation for the probability of transmission of new infections was based on the population size, number of infectious events, and the number of infectious doses per event. The model only considered females because of the lack of support for the male role in transmission and the disease's affect on males. The model divided the population into three age classes (calves, yearlings, adults), with vital rates determined by age class and disease status.

The individual-based approach allowed for a wider breadth of management options to be considered. This two-species model considered both elk and bison with an overall goal of identifying and quantitatively evaluating the most effective strategies for controlling or eradicating brucellosis (Gross et al. 1998) in the Greater Yellowstone Area. Potential methods included different rates of immunization, test and slaughter, and habitat alterations, which affected winter-feeding location of animals.

For bison, high (60%) and sustained levels of calf vaccination would be required to eradicate brucellosis, but a level of 30% would reduce seroprevalence by 50 percent. Test and slaughter only had the potential to reduce seroprevalence when implemented on large proportions of the population. Model simulations demonstrated that either vaccination or test and slaughter alone would most likely be ineffective, but combining the two would be beneficial. By considering both species, the model predicted that calf vaccination and test and slaughter programs were of limited value in eradicating brucellosis.

The model was sensitive to fetal decay rate, the proportion of infected calves born to infected mothers, and the proportion of infected females that were still infectious after giving birth or having an abortion. The model was surprisingly insensitive to the rate of abortions. The limited amount of data on the probability of vertical transmission and the likelihood of infected cows remaining infectious after abortion or parturition were two sources of uncertainty in parameter estimates.

The Interagency Bison Management Plan (2000) used a stochastic model to examine population and disease dynamics of bison in Yellowstone. A simple stage-structured

population model was combined with a disease classification framework (Anderson and May 1991) to model the response of bison to management actions. The model was developed using available information on bison demography and brucellosis to evaluate the effects of proposed management alternatives. Changes in the abundance of animals in each stage and disease class were tracked through time. The model provided a framework for organizing and synthesizing information, and enabled the consideration of multiple influences on the bison population.

Initial model parameters and settings strongly influence the trajectories of model projections. Therefore, initial conditions were specified for each management alternative and results of each alternative could then be compared. The model was initialized by categorizing bison into three age classes: 1) calves one year or less; 2) yearlings >1 year but < 3 years old; and 3) adults ≥3 years old. Model results were presented for 15 years, the life of the Interagency Bison Management Plan, and an additional three years prior to the initiation of the plan. The model was run on a yearly time step. The proportion of bison leaving the park was based on autumn population size and winter severity. Within each of the eight alternatives presented in the Interagency Bison Management Plan, residents and migrants were subjected to removal strategies. The model was updated for bison surviving into the spring and the new calves born following management. The model predicted the number of animals in each age class every autumn after management actions and reproduction.

The stochastic component of the model refers to the influence winter severity, measured in snow water equivalents, has on population dynamics and brucellosis seroprevalence within each of the management alternatives. Brucellosis seroprevalence in Yellowstone bison was addressed after spring births. Bison were categorized into four disease classes: susceptible, infected, recovered, and vaccinated. Model projections were based on vaccination rates for calves at 75%, vaccine efficacy of 70%, and reinfection of bison by elk at a rate of one case in 15 years.

The results of this stochastic model were only intended to make comparisons among management alternatives and did not include many ecological components. The model assumed there was no vertical transmission or increased mortality from infection. Transmission was also assumed to occur through abortions in early winter (January/February), prior to the management actions and natural mortality that generally occur during March and April. The model assumed that only the infected class of bison could transmit *Brucella*. Peterson et al. (1991) indicated that abortion rates in bison approach zero after the animal has been infected for two years. Therefore, bison that are no longer having abortions are unlikely to transmit the disease and were considered recovered in the model for the Interagency Bison Management Plan.

The model predicted decreases in seroprevalence and bison removals (e.g., slaughtered, hunted, or quarantined) over the life of each alternative. The modified preferred alternative in the Interagency Bison Management Plan emphasized adaptive management that involved capturing and shipping seropositive bison to slaughter, while keeping seronegatives in the population or quarantining them. A reduction in seroprevalence would be achieved through calf vaccination and seroprevalence was estimated to decrease by 63% in the first 11 years of the program.

Components of Our Approach

Our increasing knowledge base of brucellosis dynamics in Yellowstone bison is reflected in the evolution of the associated models. We have constructed our model using

recent and relevant brucellosis information and used the previous modeling efforts as a foundation. Our method builds upon previous efforts by addressing new aspects of the disease identified in the literature (Table 1). Three unique aspects of our model are the inclusions of (1) a transmission function that incorporates bison social structure and field observations relevant to exposure, (2) adult latency and recrudescence, and (3) detailed vaccine efficacy and duration of protection.

Social Structure

The potential impact of bison social organization on infection and transmission has not yet been considered. The gregarious nature of bison may influence brucellosis transmission through effects on group size, composition, and cohesion. We chose to consider social organization as an important, but unexplored, component of disease transmission.

The effect of an interaction between social structure and movement on disease transmission is not well understood, but could facilitate transmission through the clumping of individuals into social groups (Gudelj et al. 2004). At high levels of bison group cohesion, *B. abortus* may be patchy in space, thus reducing the likelihood that all individuals are equally likely to be exposed to the disease. Important components for understanding brucellosis transmission and persistence involve the mechanisms influencing formation and maintenance of bison social groups.

A primary determinant of group size is the structure of available habitat. Whether a result of increased predation risk, differential resource availability, or increased ability to maintain contact with others, group size tends to get larger as habitat becomes more open and vice versa (Rutberg 1984*a*). Seasonally changing climatic conditions influence habitat availability and affect the size of bison social groups. Winter aggregations of bison tend to be smaller due to crowding in feeding craters. Group size generally increases during the spring calving season, and summer aggregations are the largest because of the addition of males during the rut (Rutberg 1984*a*). *Brucella abortus* is believed to be transmitted entirely by pregnant bison. Thus, group dynamics between mid-gestation and parturition likely influence transmission rates.

Information on bison group stability is lacking, but the fundamental social unit is believed to be the cow-calf association (Green et al. 1989, Lott 1991). This association persists for approximately nine months in male calves and 14 months in female calves (Lott 1991). There is uncertainty concerning the extent of post-weaning association between cows and their calves. Some evidence suggests that mothers and daughters form attachments lasting until daughters reach sexual maturity (Green et al. 1989). However, other evidence suggests that post-weaning associations between cows and their calves are random (i.e., a calf is no more likely to associate with its mother than with some randomly chosen individual; Lott and Minta 1983, Lott 1991). Yellowstone bison appear to have a dynamic social structure with fluid movements between groups (Aune et al. 1998).

There is little evidence to support the hypothesis that groups of related females form lifelong associations (McHugh 1958), but bison may form nonrandom aggregations based on other factors. For instance, cows with calves tend to be found more often in groups with other cow-calf pairs than in groups with barren females (Rutberg 1984*b*). However, group stability as a whole is thought to be low (McHugh 1958, Lott and Minta 1983, Rutberg 1984*a*, Lott 1991).

Our consideration of social structure provides a unique way in which our model is different from previous modeling efforts. We do not assume that every individual in the population is equally likely to contract brucellosis. If the association among cows is not random, an individual's chance of contracting the disease is influenced by the infection status of its associates. The ability of the *Brucella* pathogen to spread is also influenced by social organization and group cohesion.

Adult latency and Recrudescence

We assumed that infected animals never completely recover from infection and modeled an adult latent class that had progressed beyond the abortive phase of infection (acute infection). These latent bison can recrudesce at a specified probability and shed *B. abortus* during live births. We included this component in the model to address how *Brucella* might be maintained at such high seroprevalence in the absence of observed abortions.

Vaccination

We included a detailed approach to vaccination by addressing vaccine efficacy and duration of vaccine protection. We included parameters that addressed vaccine effectiveness (i.e., the ability of the vaccine to protect against infection and shedding of *B. abortus*) and the duration of protection (modeled as a process of declining vaccine efficacy in years following vaccination). This method provided a comprehensive approach to modeling the effect of vaccination.

Individual-based approach

The need to make management decisions despite uncertainty makes models insightful tools into how systems might change under specified management actions. Changes at the population level can only be understood through the properties and behaviors of individuals, thereby making individual-based models valuable tools for testing predictions at both the individual and population level (Grimm and Railsback 2005). The complexity of applying vaccination efforts to influence brucellosis dynamics requires an understanding of infection at the individual level and individual-based models can help explain infection at the population level through the interactions of individuals.

To evaluate management alternatives aimed to reduce brucellosis seroprevalence in Yellowstone bison, we created an individual-based model to simulate the system under different management scenarios. The model was built in three phases: 1) synthesize current data and literature describing host-pathogen relationships; 2) construct a model with parameters estimated from empirical studies and available data; and 3) incorporate management options and analyze their influence on brucellosis dynamics.

METHODS

Model Overview

We developed an individual-based model using MATLAB 7 to evaluate the effectiveness of vaccination strategies aimed at reducing brucellosis infection in Yellowstone bison. Our methodology was similar to classic epidemiologic approaches (SIR: susceptible, infected, and recovered), but in our model bison never truly recovered from the disease. Bison were categorized into susceptible, infected, latent, and vaccinated disease classes that were tracked through the life of each individual. Changes in disease states for the overall population were evaluated under three different

vaccination scenarios. The vaccination strategies included: 1) Alternative A: boundary management through the testing, removal, and vaccination of bison migrating outside the park; 2) Alternative B: boundary and remote vaccination using biobullet delivery to female calves and yearlings; and 3) Alternative C: boundary and remote vaccination of all female bison. The disease class of individuals was changed based on events (e.g., exposure, vaccination) and rules associated with their current state (e.g., disease class, pregnancy status, vaccination status; Figures 1-4). The model used a yearly time step to follow changes in disease states of individuals throughout their lives and daily time steps to detail the processes influencing changes in disease status. Events occurring in the yearly time step included bison mating, natural mortality, exposure to *B. abortus* via elk, and management operations. The daily time step detailed the processes (e.g., infection, exposure) leading to transmission of *B. abortus* among Yellowstone bison. The individual-based model tracked information on each bison born into the population. Demographic, life history and management-related information (e.g., age, sex, social group, disease status, reproductive status, reproductive output, vaccination status, and management removal) were monitored for each female bison. The individual-based model consisted of three general components: 1) model initialization; 2) yearly processes; and 3) daily processes (Figure 5).

Model Initialization

Model parameters (Table 2) were initialized prior to running the model. Management options were set to simulate desired management vaccination scenarios under specified levels of vaccine effectiveness. Uncertainty regarding vaccine efficacy and duration of protection required running model projections for these parameters over a range of values to address their sensitivity. Each bison was assigned to a social group during initialization. The number of social groups was determined by the initial population size and maximum and minimum group size values set in the parameter block. Bison were provided with demographic information (i.e., age, sex) and assigned to a disease class (i.e., susceptible, infected, latent). Age was assigned using estimates of bison population age structure (1-15 years) and sex was assigned assuming an equal sex ratio. Bison were given a disease classification based on estimates derived from seroprevalence data. Bison social groups were then subdivided into maternal units. Calves were assigned to mothers making the cow-calf group a maternal unit. Maternal units were then monitored as well as individual animals.

Yearly Time Step

The yearly time step began with bison becoming pregnant based on estimates of age-specific pregnancy rates. Pregnant bison were given either a pregnancy date or an abortion date depending on the individual's disease class. The abortion period included the last trimester (90 days) of gestation (287 days) before the live birth period (61 days; Berger and Cain 1999). Infected bison will most likely abort their first pregnancy after infection and were given an abortion date, while susceptible and latent animals were given a live birth date. Pregnant animals in the infected class were scheduled to abort their next pregnancy after infection at a high probability (0.96). Otherwise, they had an infectious live birth. The model then initiated the daily process simulating transmission occurring near parturition. The model continued with the yearly processes when the days loop was completed.

Daily Processes

Influence of Disease State on Pregnancy

Daily processes involved breaking up maternal units by weaning calves reaching their dispersal date, which was prior to their mother having a second calf. Weaned male calves were removed from further model processes, but were included on yearly model outputs. Pregnant bison having a due date for the current day had a live birth, an infectious live birth, or a brucellosis-induced abortion, depending on the cow's disease state. Susceptible bison had a non-infectious live birth unless exposed to B*rucella* during pregnancy. *Brucella abortus* needs to incubate for a predetermined time to induce an abortion in newly infected, pregnant, susceptible bison. If there was insufficient incubation time (<35 days, Gross et al. 1998) before parturition, then the cow had an infectious birth with a set probability (0.66; Gross et al. 1998) that the newborn calf was infected through vertical transmission. Infected bison aborted their pregnancy at a specified probability (0.96; Olsen et al. 2003) or had infectious births with the previously mentioned probability of vertically transmitting the disease to the newborn calf. Pregnant, latent cows had a non-infectious birth unless they recrudesced (i.e., relapsed to the infectious state; $p = 0.05$). Recrudescing cows had an infectious birth with the previously mentioned probability of vertically transmitting infection to the newborn calf.

Exposure and Transmission

Infectious events (i.e., abortions and infectious live births) were modeled as horizontal transmission events that shed *Brucella* onto the landscape. Transmission involved the exposure of maternal units (Figure 6) that were either cows and their newly-born calves or single female bison (≥1 year old). We assumed that the maternal unit was the fundamental social unit and if the cow was exposed to *Brucella*, then the calf was also likely to be exposed. An exposure of one maternal unit per infectious event was observed to fit within the range of historic seroprevalence data (Figure 7). Field observations of bison group members interacting with new born calves and birth tissues suggest cow-calf pairs approach parturition sites together. The number of maternal units exposed per infectious event was decided randomly by drawing from a Poisson distribution best fitting field observations of potential exposure (i.e., group members licking newborn calves and birth material). For field data, parturition served as an observable event beginning with birth material protruding from the vaginal opening and ending when newborn calf, birthing cow, and bison group moved off the birth site. The sample space included contact with birth material or no contact. Contact was treated as a discrete random variable and a Poisson distribution was fitted to the frequency of contact (Figures 8 and 9). The rate parameter ($\lambda = 1.42$) that best fit the field data was adjusted ($\lambda = 1.0$) to better fit estimated population seropervalence estimates (Figure 10). Only maternal units in the susceptible class changed their disease state (i.e., susceptibles became infected) when exposed. Infected and latent class bison remained in their current disease state following exposure. The exposure distribution was used to decide the number of exposures for each infectious event. The exposure potential (group interactions) following a *Brucella*-induced abortion has never been observed in Yellowstone. We assumed that field observations of bison interacting with newborn calves and birth tissues were similar to abortion events and were treated equally in the model.

Social Groups and Transmission

The model tracked bison groups as well as individuals. Long-term group size information for Yellowstone bison (McHugh 1958) was used to divide the population into groups of cows and their calves. Social groups of 24-40 females and calves (McHugh 1958) were assumed to have greater contact with each other than with bison outside their group. Bison groups on the Yellowstone landscape may be separated by many miles. Thus, the probability of exposure following an infectious event was expected to be greater within groups than between groups.

To investigate the potential effect of known bison social linkage (cow-calf bond), we used a parameter (β) as a multiplier accounting for the higher probability of exposure occurring within a bison's own group. As stated earlier, the number of exposures per infectious event was drawn from a Poisson distribution ($\lambda = 1.0$) based on field observations and estimated population seroprevalence. The specific individual bison (maternal units) exposed were determined using a biased random draw from the population. The parameter β biases the exposures in favor of bison within the social group where the infectious event occurred. The probability that a maternal unit in all groups, other than the group containing the infectious event, was exposed to brucellosis was expressed using Equation 1:

$$(1) \qquad \frac{N_i}{\beta(N_k - 1) + \sum_{j=1}^{n} N_j}$$

where N_i and N_j are the number of maternal units in groups *i* and *j*, N_k is the number of maternal units in the abortion group, and *n* is the number of groups. The probability of a maternal unit in the abortive group contracting the disease was expressed using Equation 2:

$$(2) \qquad \frac{\beta(N_k - 1)}{\beta(N_k - 1) + \sum_{j=1}^{n} N_j}$$

Continuing Yearly Processes

After completing daily operations, the remaining yearly functions were continued. Social groups and their maternal units were reestablished based on group size criteria. Groups growing beyond set limits had maternal units transferred randomly to form new groups or supplement existing groups. Bison were then subjected to natural mortality based on estimated age-specific death rates. Mortality was slightly higher for infected and latent class individuals to account for the pathogen's small contribution to the death rate (Dobson and Meagher 1996).

Boundary Management Operations and Vaccination

Management criteria (i.e., test, remove, vaccinate) were used in all three vaccination strategies we modeled. In any given year, a proportion of the Yellowstone bison population will attempt to move beyond the park boundaries. Bison can potentially be hazed back into the park, but the number of captured animals is largely a management

decision. We determined the number of bison that might be handled during boundary operations in a given year using information on boundary captures during the past 20 years (1985-2005; Table 3). We used three intervals (< 0.1, 0.1-0.2, 0.2-0.3) representing proportions of the population, and the frequency that captured bison fell within those intervals, to decide how many bison might be captured in a given year.

Based on the sensitivity and specificity of the fluorescence polarization assay, we assumed that infected and latent bison could be correctly diagnosed as seropositive during 100% and 95% of the tests, respectively. These seropositive bison were removed from the model to simulate management operations. The remaining seronegative bison were vaccinated and assigned vaccinated status based on the specified efficacy of the vaccine. These vaccinated bison were protected from infection if exposed to *B. abortus* based on the level of vaccine efficacy. Simulations were run over a range of vaccine efficacy values under each management alternative. Vaccinated bison that were subsequently exposed to *B. abortus* were protected from infection, but would still react positively on serologic tests and, consequently, be removed during management operations. We recorded the proportion of these seroposive-vaccinants in the model under each alternative. Bison previously exposed to *B. abortus* (i.e., infected and latent class bison) remained in their original states if vaccinated. The vaccine SRB51 was not expected to offer lifetime protection and the expected duration of protection in Yellowstone bison is unknown. We included a duration-of-protection component to vaccine efficacy, which allowed for modeling a declining level of vaccine protection in years after vaccination.

Elk Transmission

Elk populations in the Greater Yellowstone Ecosystem are also infected by brucellosis, and have been implicated as the vector of brucellosis infection to cattle herds in Idaho, Montana, and Wyoming. The pathology of the disease in elk is believed to be similar to that of bison and cattle. We included elk as a potential source of brucellosis infection for bison and modeled exposure from elk at a low probability (0.01).

Model Outputs

The yearly functions concluded by outputting all relevant information for each year. The data were then analyzed over a 30-year period and comparisons were made between the three alternatives. The following four rates were used to assess the effectiveness of each vaccination strategy: 1) decreases in seroprevalence; 2) decreases in infectious events; 3) proportion of population vaccinated; and 4) proportion of seropositive bison removed during boundary operations.

RESULTS

Model simulations were conducted to evaluate the three proposed vaccination strategies. This was accomplished by: 1) defining a default parameter set (Table 2); 2) establishing operating rules for the individual-based model (Figures 1-4); 3) assessing parameter sensitivity on the response variables of interest (i.e., seroprevalence, infectious events, vaccinated bison, and removed bison); and 4) evaluating the effectiveness of each management alternative. Sensitivity of response variables were investigated by varying vaccination parameters within specific management scenarios. Each vaccination strategy was evaluated by running multiple model simulations to address the variability of stochastic model processes.

Default Parameters and Sensitivity Analysis

The mean number of exposures occurring per infectious event is an uncertain parameter with a high degree of sensitivity. Simulations conducted with different exposure levels allowed us to select exposure values for the default parameter set that best fit estimates of brucellosis seroprevalence in the bison population. An exposure value of one exposure per infectious event resulted in an average population seroprevalence of 51% over 100 years (Figure 7). This value provided bison seroprevalence projections that best fit within the estimated 40-60%. We incorporated field data to fit a Poisson distribution ($\lambda = 1.0$) that best fit our current seroprevalence data. The fitted distribution was consistent with field observations in that a high proportion (>0.3) of infectious events resulted in zero exposures.

The trajectories of response variables varied under each of the management scenarios (Figure 11-13). Sensitivity to different levels of vaccine efficacy was more pronounced in alternatives with higher vaccination effort (Alternative C). Model trajectories demonstrated more annual variability in Alternatives A and B that had less vaccination effort. There was a greater decrease in the level of population infection (seroprevalence) when remote vaccination was included in the alternatives. The proportion of infectious events (exposure sources) was reduced to the lowest level in Alternative C, which also resulted in the greatest proportion of vaccinated bison in the population. Boundary removals resulting from migrations out of the park were stochastic, but the trajectory of decrease was most pronounced in Alternative C.

Simulations of Management Alternatives

Ten simulations were conducted at intermediate levels of vaccine efficacy (0.5) for each of the three management alternatives: 1) boundary vaccination of female calves and yearlings (Figure 14a-e); 2) combination of boundary and remote vaccination of female calves and yearlings (Figure 15a-e); and 3) boundary vaccination of all females (Figure 16a-e). The strategies that combined boundary and remote vaccination (Alternatives A and B) provided the largest reduction in brucellosis infection (seroprevalence). The strategy focusing remote vaccination efforts on all female bison (Alternative C) provided the greatest decreases in seroprevalence. Under Alternative A, seroprevalence decreased by 24% (0.46 to 0.35) over the 30-year period with 1% of the population vaccinated. Under alternative B, seroprevalence decreased by 40% (0.47 to 0.28) over the 30-year period with 10% of the population vaccinated. Under alternative C, seroprevalence decreased by 66% (0.47 to 0.16) over the 30-year period with 29% of the population vaccinated. Model simulations showed the greatest correlation between decreasing seroprevalence and the proportion of vaccinated bison in alternatives including remote vaccination (Figure 17a-c). The larger proportion of vaccinated bison under Alternative C resulted in the greatest reduction of infectious events among the 3 alternatives. The trajectory of bison removals was also less variable and decreased further under Alternative C compared to other alternatives. The proportion of seropositive-vaccinates (i.e., vaccinated bison that were subsequently exposed) was larger under Alternative C than Alternatives A and B. Population growth trajectories had the greatest increase under alternatives with greater vaccination effort (Figure 18).

A breakdown of seroprevalence into its component classes (infected and latent) was conducted in female bison. Infected and latent bison react positively on serologic tests and comprise the total seroprevalence for the population. Seroprevalence levels were

found to be much higher and decreased at a greater rate than the infectious component of the population (Figure 19).

Simulations were conducted to identify the effect of decreasing levels of vaccine efficacy after vaccination on seroprevalence for each alternative. Decreasing efficacy levels (0.10, 0.20, and 0.30 per year) simulated a decrease in the duration of vaccine protection in the years following immunization (Figure 20-22). The decreasing level of protection had the most pronounced effect on the alternatives with higher levels of vaccination effort (Alternative C).

Simulations were conducted to better understand the response of infection under a short-term implementation of Alternatives A and C. Vaccination strategies were conducted for 10 years, after which all vaccination and management activities ceased. Responses were modeled across vaccine efficacy levels (0.10, 0.30, 0.50, and 0.70). Seroprevalence returned to pre-vaccination levels for both alternatives (Figures 23a and 24a). The rate of return was more sensitive to the level of vaccine efficacy for Alternative C than Alternative A. The level of vaccinated animals decreased toward zero as individuals were removed from the model based on natural mortality rates (Figure 23b and 24b).

DISCUSSION

Model simulations identified that a vaccination program combing remote vaccination with boundary management will be far more effective than boundary management alone (Figure 25-27). A consistent long-term investment in vaccination will be required to meet the objective of the Interagency Bison Management Plan for reducing brucellosis transmission risk to cattle by reducing infection within Yellowstone bison. A level of acceptable risk has not been articulated, but model simulations indicate that brucellosis infection, as indexed by seroprevalence, can be substantially reduced with a vaccine of intermediate efficacy and realistic remote vaccination effort. A remote vaccination program targeting all female bison in the population (Alternative C) would best accomplish this objective (Figure 28). The effectiveness of Alternative C lies in focusing vaccination efforts on all segments of the population that may potentially contribute to infection and transmission.

Remote vaccination extends the reach of management and allows for considerably more animals to be protected from infection than vaccination during boundary management alone. Thus, the success of effectively reducing seroprevalence levels in Yellowstone bison will rely on including remote vaccination. Model simulations suggest that boundary management can be effective at reducing population growth rate, but will provide only a small decrease in brucellosis infection. This finding can be attributed to the low vaccination rates that rely on out-of-the-park migrations. Simulations involving only boundary management were less sensitive to vaccine efficacy because very few animals were receiving the vaccine. As more bison are vaccinated, the sensitivity of vaccine efficacy becomes more pronounced. Vaccine efficacy provides protection from acquiring infection and subsequent shedding of the bacteria. Increasing the level of vaccine-protected bison reduces the amount of infectious material shed onto the landscape and reduces the likelihood of horizontal transmission. As a result, fewer animals are exposed and the number of seropositive bison removed at the boundary decreases. Model simulations demonstrated that the interconnectedness of these variables was dependent on vaccine efficacy and vaccination effort. Vaccine efficacy

improvements may take some time and increasing vaccination effort may compensate for less than desirable vaccine efficacy in the short term.

The current vaccine, SRB51, is unlikely to provide lifetime protection. Therefore, targeting all female bison will allow animals to receive multiple vaccinations that extend the duration of vaccine protection. This will aid in reducing uncertainty of protection in years following immunization. By targeting only young animals for vaccination, we increase variability in declining seroprevalence because the level of vaccine protection is likely to decrease as the animal ages. The expanded target class of Alternative C allows for extending the duration of protection by providing booster vaccinations in future years.

Reducing the level of infection in bison does not eliminate the risk of brucellosis transmission to cattle, and concerns over co-mingling will require management intervention at Yellowstone boundaries. Testing bison at boundary capture facilities will provide valuable insights into the effectiveness of the vaccination program. Currently, seroprevalence is the only indicator available for measuring the state of infection in the population and is likely to provide inflated levels of true infection and risk. Additionally, vaccinated bison that are subsequently exposed to field strain *Brucella* will react positively on serologic tests. These bison may be protected from infection, but would be removed during boundary operations. Model projections estimate this number be < 2% of the population and 4% of females. These bison play an important role in herd immunity by reducing the number of exposures of susceptible bison during an infectious event.

Model simulations demonstrated an increase in seroprevalence as vaccinated bison were removed through natural mortality under short-tem vaccination scenarios. Even under high levels of vaccine efficacy, investment in short-term vaccination efforts will not reach long-term goals of reducing brucellosis infection in bison. Vaccination is likely to be a constant, long-term investment with the tools (i.e., vaccine, delivery method, and diagnostics) currently available. Reductions in the level of infection can be achieved, but will require a strong surveillance program to validate the corresponding decrease in infection with vaccination effort.

Model Uncertainty and Information Needs

Vaccine Efficacy

Vaccine efficacy is an important parameter with much uncertainty. The effectiveness of SRB51 has not been tested under field conditions similar to Yellowstone. The effectiveness of RB51 against *B. abortus* within Yellowstone bison is largely unknown and research is needed to estimate RB51's efficacy within the Yellowstone system.

Remote Vaccination

Currently, remote vaccination via biobullet delivery is the proposed method of vaccinating Yellowstone bison. This delivery method has been validated under experimental conditions, but its effectiveness has not been evaluated within the Yellowstone system. Mock vaccination trials (R. Wallen, National Park Service, unpublished data) have simulated remote vaccination operations in the field, but have not contacted bison with the projectile. Realistic group responses to vaccination are largely unknown. The stress and annoyance of remote vaccination may result in bison behavior making them difficult to vaccinate with this method. Research is needed to validate how free-ranging bison might respond to vaccination. Remote vaccination effort will be unable to compensate for vaccine efficacy if bison are difficult to vaccinate.

Duration of Vaccine Protection

The duration of vaccine protection offered by SRB51 is unknown, but undoubtedly plays an important role in preventing infection and transmission. Yellowstone bison experience strong seasonal changes that cause stress and a reduction in nutritional condition. How bison respond to vaccination under these conditions will be important for estimating responses to exposure after vaccination.

Vertical Transmission

The large proportion (0.5) of young, immature bison that are seropositive indicates that exposure to *B. abortus* occurs early in life. Little is known on vertical transmission through infected milk or trans-placental transmission in bison. The risk of this route of exposure increases the need to vaccinate reproductively mature cows to prevent mammary gland and placental infection. A greater understanding of this potentially important route of transmission will lead improved surveillance methods and parameterizing more detailed transmission models.

Latency and Recrudescence

The recovery rate from brucellosis in bison is unknown and it cannot be assumed that infected bison will eventually recover from infection (i.e., clear the bacteria). Latent carriers of *B. abortus* are well documented and the causes of recrudescence are speculative at this point. Field observations and sampling of Yellowstone bison at parturition indicate that normal birthing events can shed *B. abortus* in infected tissues. All the potential transmission routes and female age classes contributing to transmission are unclear and require further investigation.

Seroprevalence

The difficulty in monitoring the level of brucellosis infection within the population underscores the need for multiple indicators to measure the effectiveness of a vaccination program. Seroprevalence is an attractive indicator because serum is easily obtained and diagnoses are quick and simple. Most importantly, using seroprevalence as an indicator of infection does not involve killing the animal to obtain samples. Nonetheless, it should be monitored in combination with other indicators, such as bacterial culture. Seroprevalence indicates a history of exposure (i.e., antibody responses) and does not provide a complete picture of how bison may be responding to vaccination. Infection levels may be much lower than indicated by seroprevalence. Combining serology tests with culture work on the same animal will help estimate the proportion of potentially infectious animals that react positively on serologic tests. *Brucella abortus* has been positively cultured in 46% of seropositive Yellowstone bison (Roffe et al. 1999). Linking culture tests conducted on bison removed during management operations with their serology will provide a more accurate understanding of how bison are responding to vaccination and aid in brucellosis surveillance.

Conclusions

The goal of reducing brucellosis transmission risk to livestock outside the park can be best achieved by combining remote vaccination of bison with boundary management. Boundary management requires considerably less investment compared with remote vaccination, but is unlikely to produce desirable results. The most effective strategy for

reducing brucellosis seroprevalence is to remotely vaccinate all female bison. This allows bison to receive multiple vaccinations that extend the duration of vaccine protection and protect against recurring infection in latently infected animals. The uncertainty in mentioned parameters and processes illuminates the need for further research. The model results suggest that initial progress might be slow because of high seroprevalence, long-lived antibodies, and the removal of vaccinated seropositive bison during boundary operations. Though vaccination is unlikely to eradicate *B. abortus* from Yellowstone bison, it can be an effective tool for reducing the level of infection. A decrease in overall infection allows for incorporating advances in the fields of diagnostics, vaccine development, and delivery into ongoing management programs. This will in turn advance the objective of the Interagency Bison Management Plan for reducing brucellosis transmission risk to livestock while conserving Yellowstone bison.

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Tables and Figures

Table 1. Comparisons of approaches of previous brucellosis models

Model Subject	Peterson et al. 1990	Dobson and Meagher 1996	IBMP 2000	Gross et al. 1998	How we addressed subject
Used Fixed Transmission Rate	x	x			We modeled transmission with a randomized process using an exposure distribution derived from field observations to decide the number of individual that will enter infected class
Used a completely recovered disease class	x	x	x		Animals never fully recovered from the disease and a select proportion of the population can recrudesce and shed *B. abortus* during live births
Threshold of disease establishment		x			Did not make any assumptions concerning disease thresholds
Assumed all individuals equally likely to contract disease	x	x	x	x	Divided population into groups consisting of cow-calf maternal units. We could adjust the probability of infection within group and between groups
Modeled Vertical Transmission		x		x	We included the probability that latent cows could pass the disease onto their offspring
Animals assumed to be infectious for set period (2 yrs)		x			Once infected animal can only move to either latent or vaccinated state with set probabilities of shedding *Brucella* in the future
Used Vaccine efficacy as a parameter	x		x		We modeled vaccine efficacy (probability vaccine will offer protection from infection) over a range of values and addressed a decline in the duration of vaccine protection in years post vaccination
Modeled elk reinfection		x	x	x	Used a parameter to model a select proportion of the bison population that will be exposed to *Brucella* by elk each year
Modeled exposure				x	Used a stochastic process to decide in what group and which maternal units in the group get exposed
Modeled stochastic processes			x	x	Much of the model uses random numbers to make decisions based on probabilities of these events occurring

Table 2. Model default parameters

Parameter/Variable	Value	Source
Pregnancy rate (Pr)		BEMO Data
• calves and yearlings 0-1	0	
• 2 year olds	0.71	
• 3 year olds	0.79	
• 4 year olds	0.76	
• Adults (5 yrs+)	0.89	
Calving rate (Cr)	0.71	BEMO Data
Birth period (Bdays)	61 days	Berger and Cain 1999
Abortion period (Adays) (prior to parturition date)	90 days	NRC 1998
Death rate (Dr)		Dobson and Meagher 1996
• 0-2yrs	0.2	(Modified for age classes)
• 3-13 years	0.1	
• 14 years	0.2	
• 15 years	1.0	
• Virulence (Brucellosis addition to death rate)	0.005	
Group size (parturition/abortion period)		BEMO Data
Min 24		
Max 48		
Disease State		BEMO 2004 and MTDOL
• Susceptible (S)	0.53	2005 Management Capture;
• Infected (I)	0.22	Calculated using Roffe et al. 1999
• Adult Latent (L) (Infected but not infectious)	.25	
Rate of recrudescence	0.05	Review of Latency Lit
Exposures per infectious event (MUs)	Poisson dist ($\lambda = 1.0$)	Distribution fitted from BEMO Data
Vertical Transmission (vxm)	0.66	Gross et al. 1998
Minimum Incubation	35 days	Gross et al. 1998
Beta (β) (social transmission factor)	1.5	Fitted parameter

Bison Captures (outside park boundary in any given yr)		**BEMO Data (past 20 yrs *1985-2005*)**
• 0-10% of population captured	.84	
• 10-20% of population captured	.11	
• 20-40% of population captured	.05	
Bison Removals at Capture Facility		
• Removal of Infected class	1.0	Nielson and Gall 2001
• Removal of Latent Class	.94	
<u>Vaccination (Injection & biobullet)</u>		Olsen 2004 USDA Draft Summary
• Vaccine Efficacy (VE)		modeled over a range of values

Table 3. Analysis of 20 years of boundary data for estimating the yearly proportion of captured and tested bison outside the park. A proportion of the bison population will move outside the park in any given year. The proportion of the bison population handled in a given year was estimated by drawing from one of 3 population intervals at the specified probabilities: 1) [0-10%, p=.76] 2) [10-20%, p = .19] and 3) [20-30%, p = .05]. The single year (1997=0.315) that over 30% of the population was handled was adjusted to maintain the yearly migration below 30%.

Year	Bison Handled	Pop size	Proportion of pop handled
1985	**88**	**2114**	**0.041**
1986	**57**	**2291**	**0.024**
1987	**6**	**2433**	**0.002**
1988	**35**	**2644**	**0.013**
1989	**569**	**3159**	**0.180**
1990	**4**	**2606**	**0.001**
1991	**14**	**3178**	**0.004**
1992	**271**	**3426**	**0.079**
1993	**79**	**3304**	**0.023**
1994	**5**	**3551**	**0.001**
1995	**427**	**3956**	**0.107**
1996	**433**	**3398**	**0.127**
1997	**1084**	**3436**	**0.315**
1998	**11**	**2105**	**0.005**
1999	**94**	**2239**	**0.041**
2000	**0**	**2444**	**0**
2001	**6**	**2800**	**0.002**
2002	**265**	**3286**	**0.080**
2003	**252**	**3880**	**0.064**
2004	**488**	**3824**	**0.127**
2005	**184**	**4239**	**0.043**

Interval	*Frequency*	*Cumulative %*
0.1	16	76.19%
0.2	4	95.24%
0.3	0	95.24%
0.4	1	100.00%
More	0	100.00%

Figure 1. VACCINATION DIAGRAM FOR SUSCEPTIBLE BISON COW

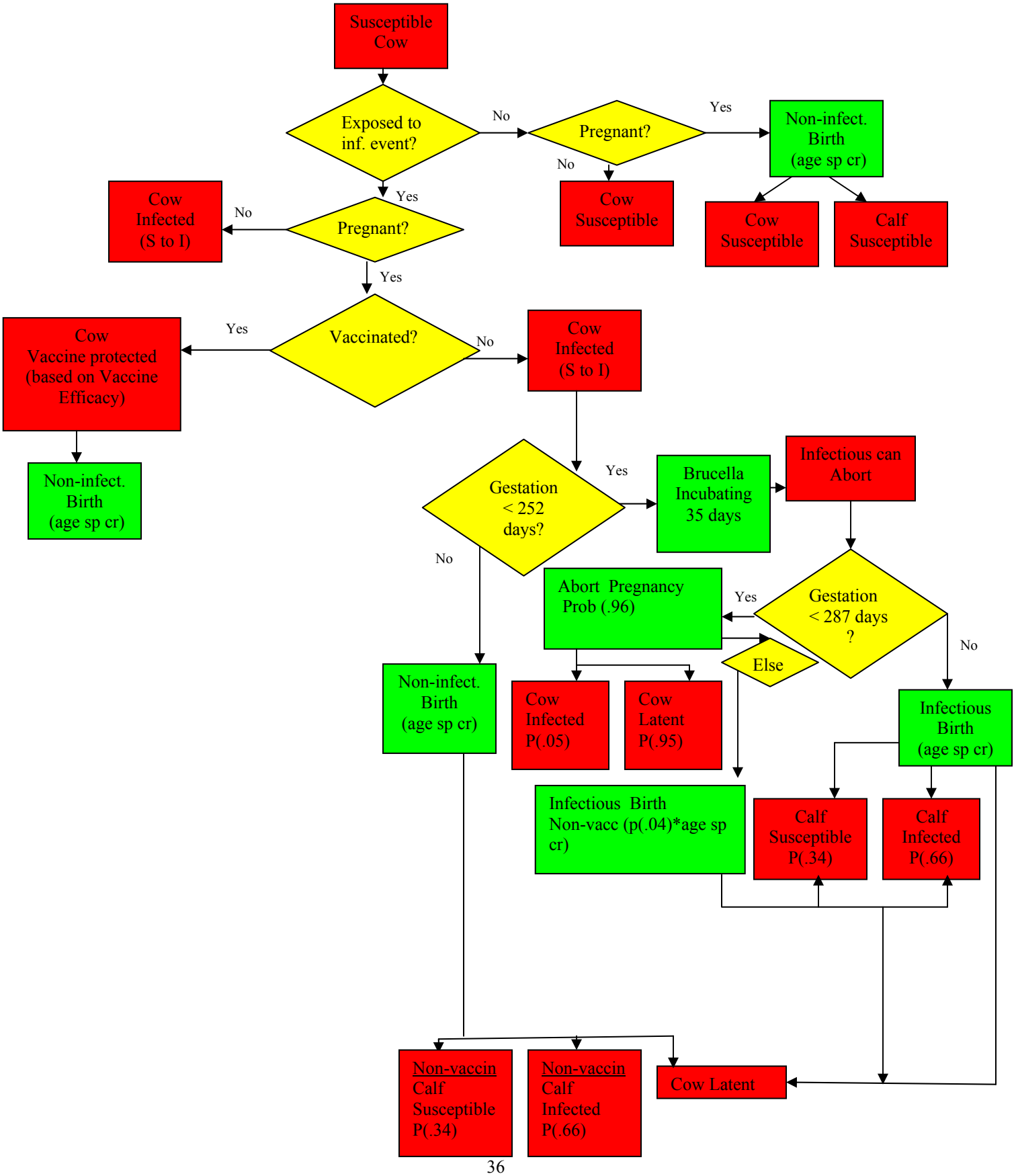


Figure 2. VACCINATION DIAGRAM FOR INFECTED BISON COW

These are bison that are already in the infected state and B. abortus has had adequate time to induce an abortion.

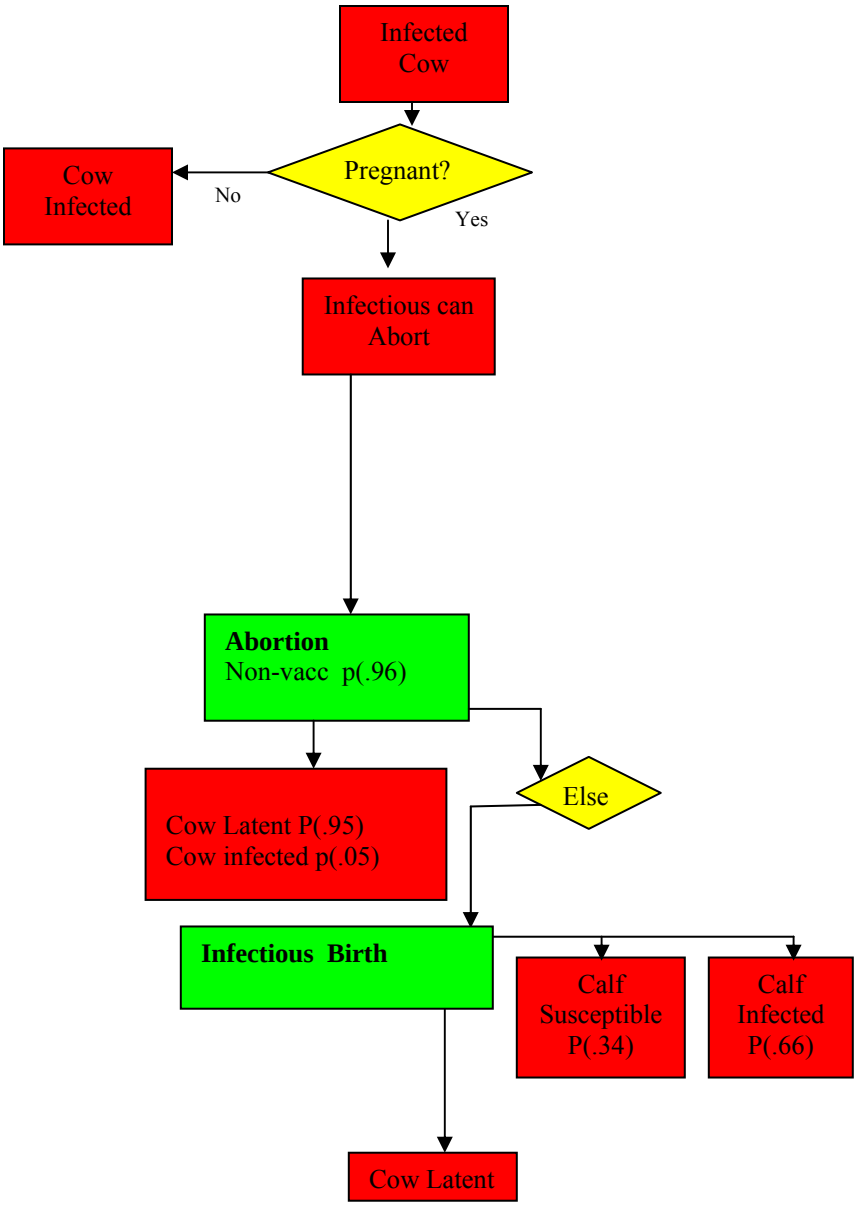


Figure 3. VACCINATION DIAGRAM FOR LATENT BISON COW

Assumptions and Rules

1. A select proportion of pregnant latent cows will relapse every year and potentially shed *B. abortus* in an infectious birth
2. Latent recrudescing cows do not have abortions

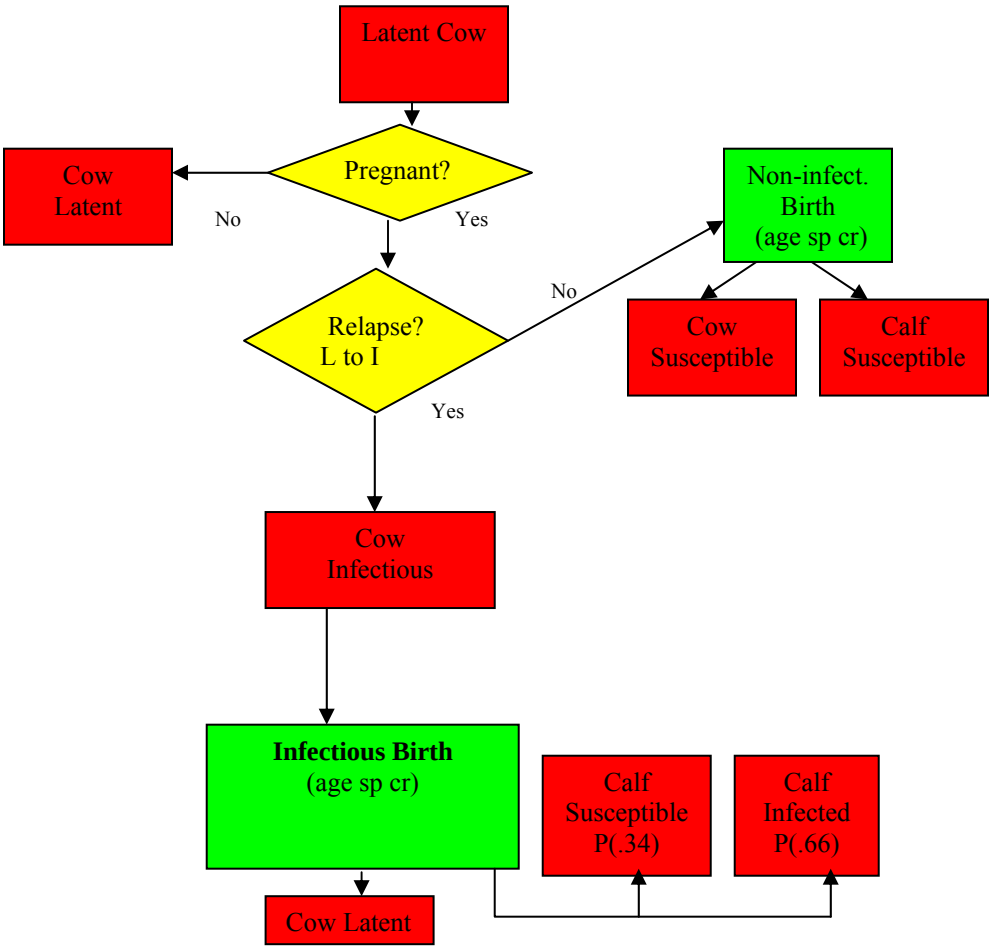
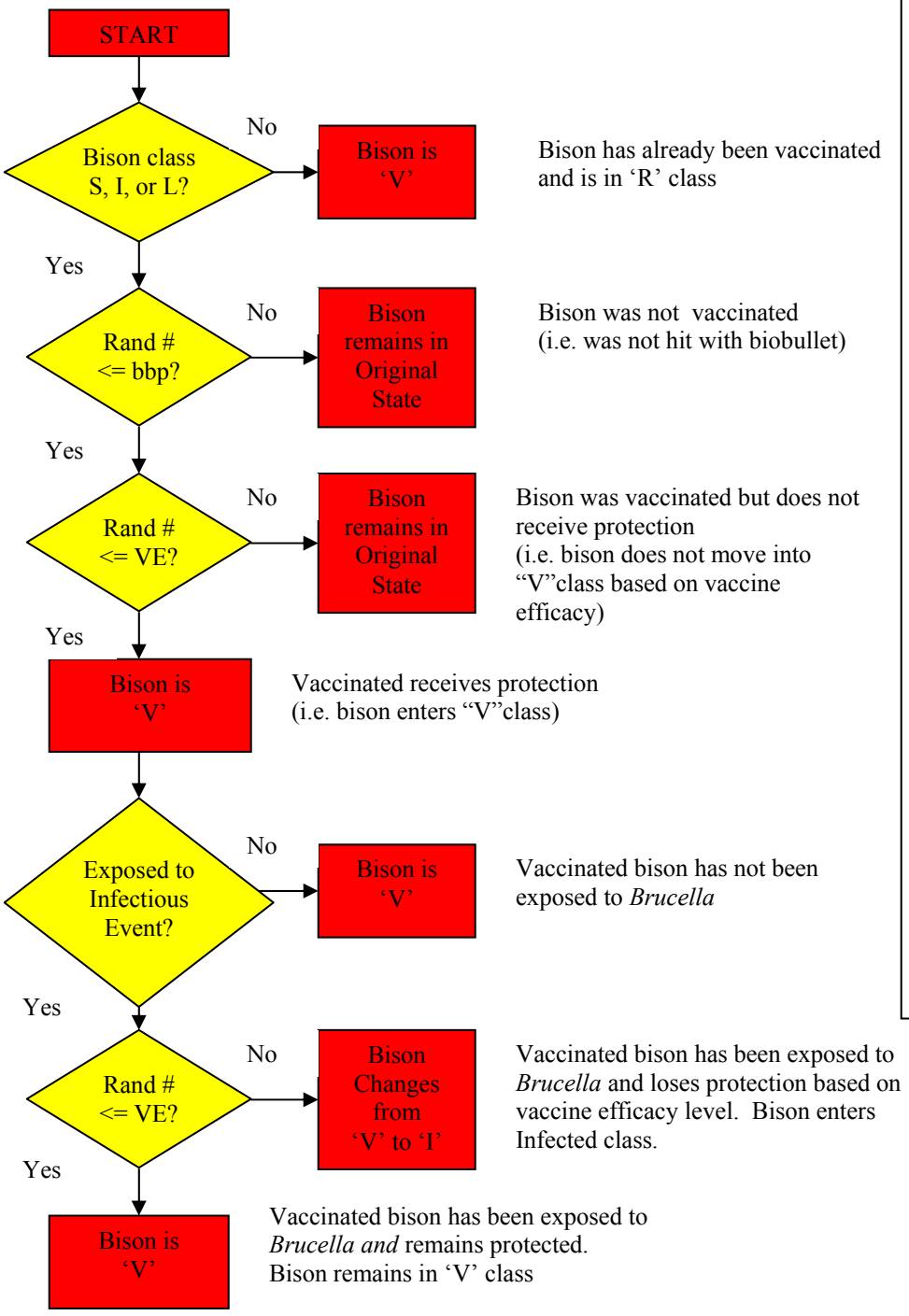


Figure 4. PROTECTION DIAGRAM FOR REMOTE VACCINATION OF BISON
This diagram provides an overview of the influence specified parameters have on short-term and long-term protection of remote vaccinated bison.



Definitions

Disease States

Susceptible (S):

- Never been exposed to *B. abortus*

Infected (I):

- Actively Infectious; high probability of shedding *Brucella* during next pregnancy

Latent (L):

- Infected, but not actively infectious; Can recrudesce and shed Brucella during future pregnancies at specified probability.

Vaccinated (V)

- Vaccinated bison that are protected from shedding Brucella

Parameters

Biobullet protection (bbp)

- Probability that target animal will receive biobullet. Estimated proportion of target class receiving vaccine

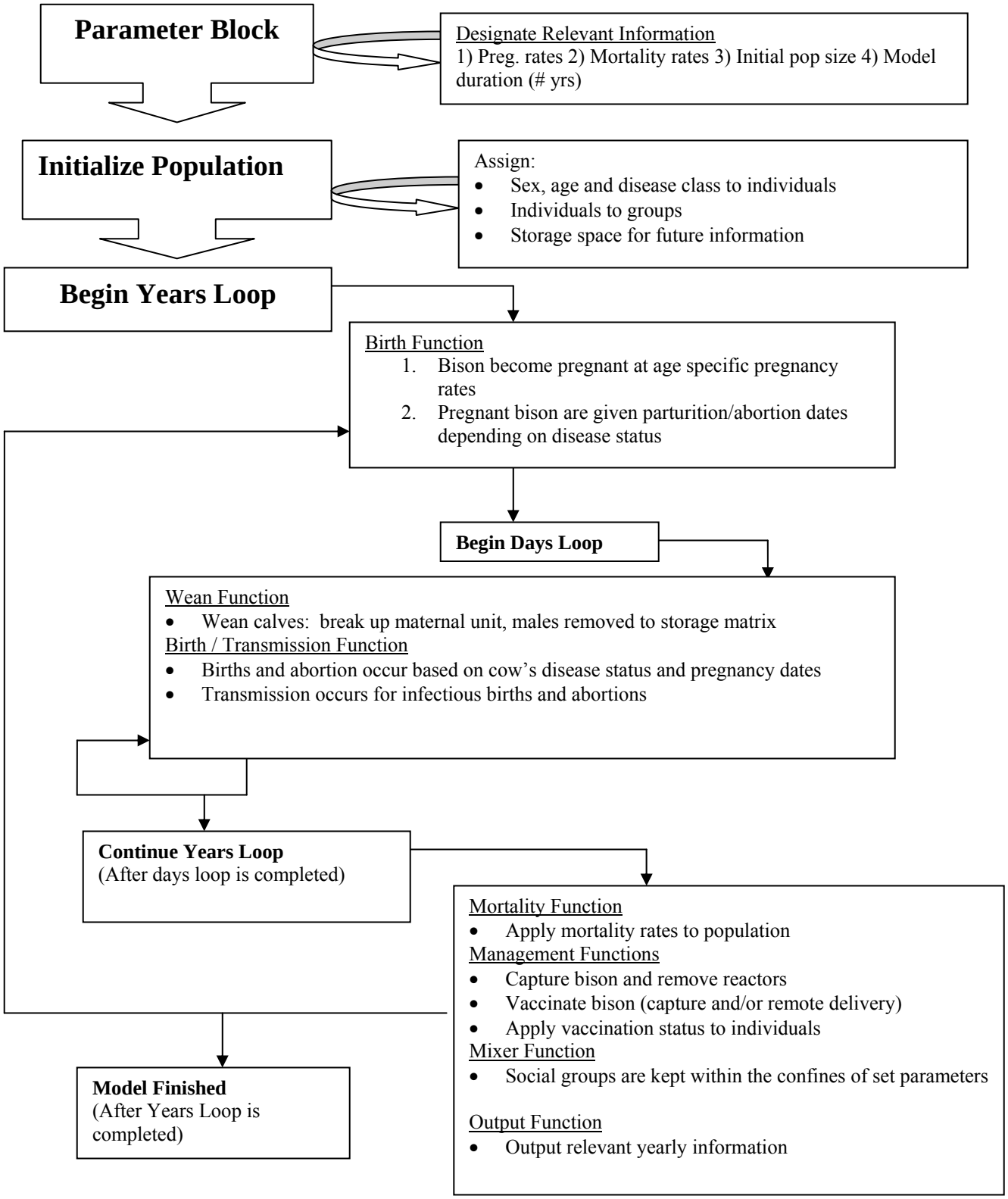
Vaccine Efficacy (VE)

- Probability bison will enter protected state (V) and remain in that state if exposed to field strain *Brucella.*

Infectious Event:

- *Brucella* induced abortion or infectious live birth. These are the 2 events leading to horizontal transmission

Figure 5. BISON BRUCELLOSIS MODEL OVERVIEW



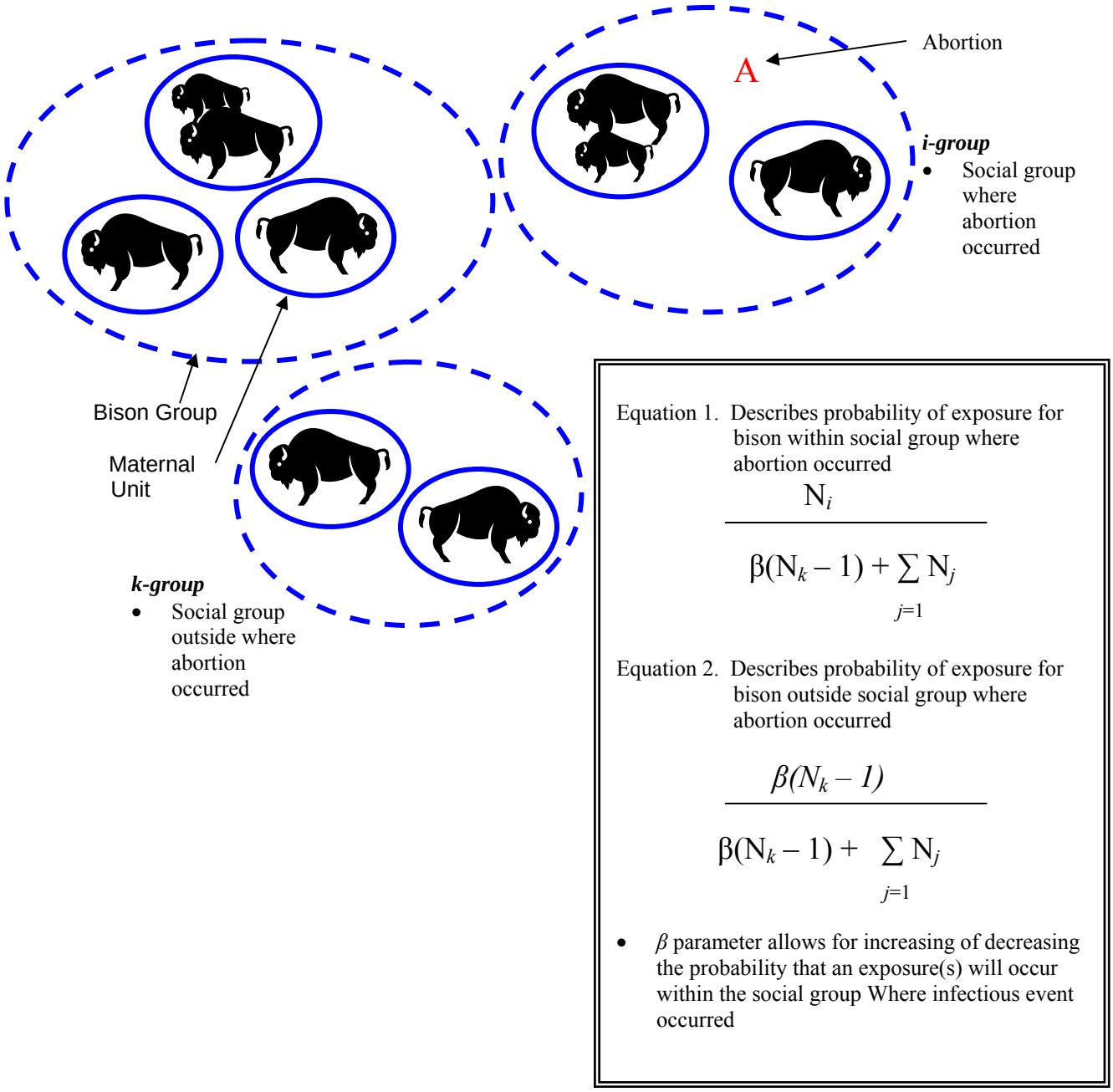


Figure 6. **SOCIAL STRUCTURE AND TRANSMISSION**

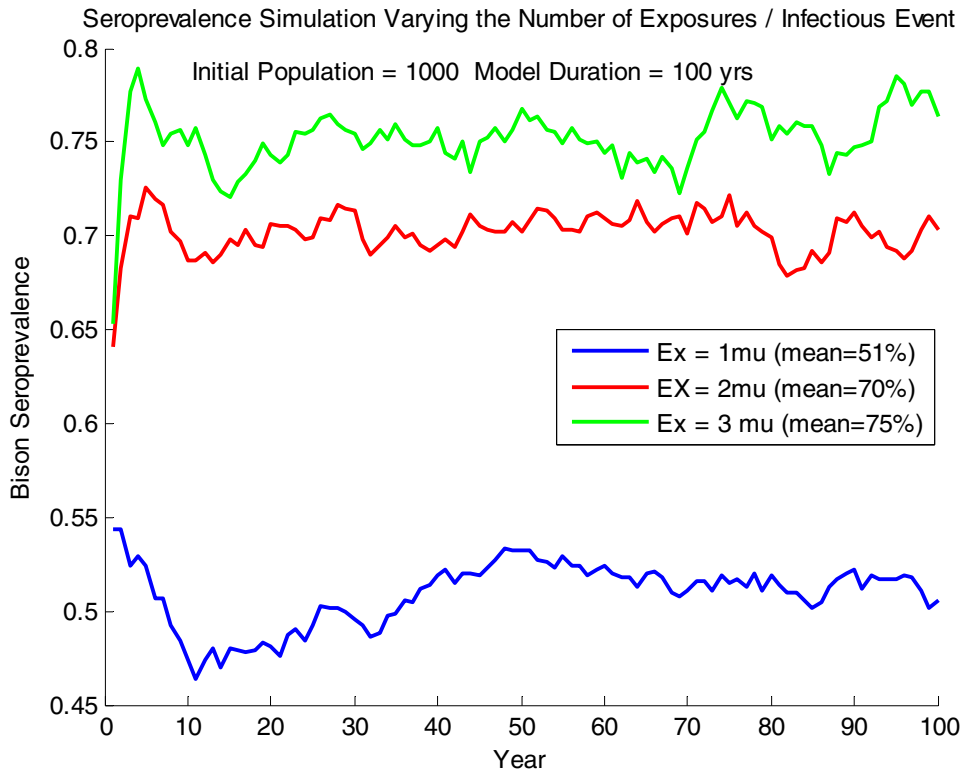


Figure 7. Simulated seroprevalence levels for different exposure parameters (maternal units) per infectious event. YNP estimated seroprevalence (40-60%) is best fit by a single exposure per infectious event.

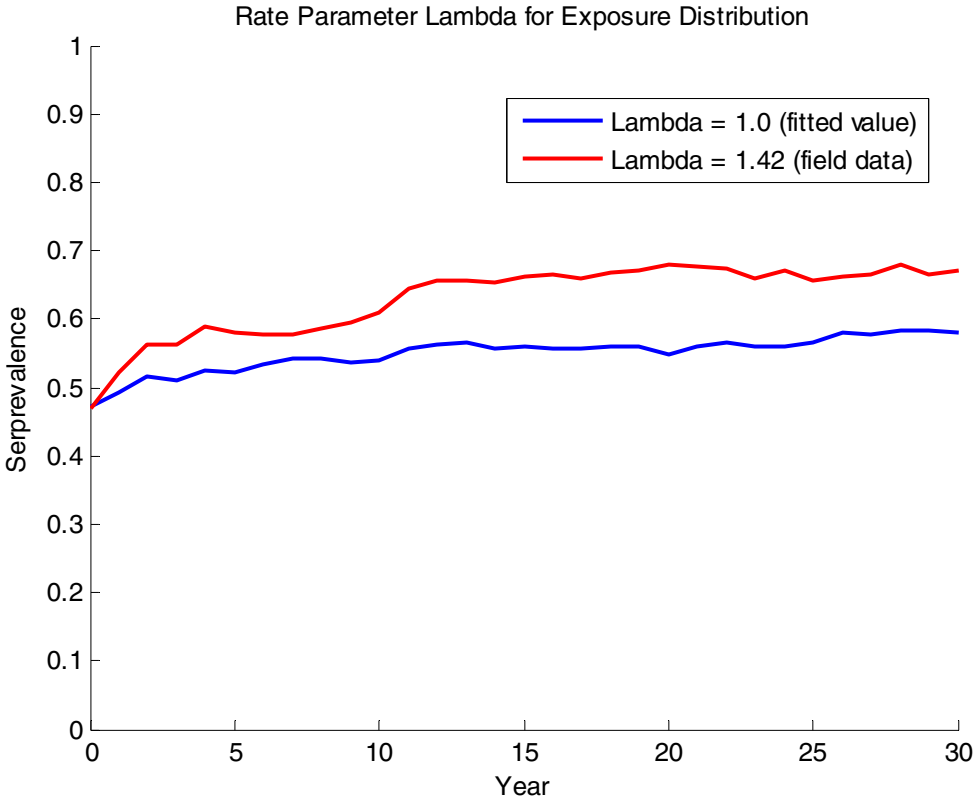


Figure 8 . Simulated seroprevalence for exposure distribution (Poisson) for 2 different rate parameters (λ). The rate parameter from field data (λ= 1.42) was adjusted (λ=1.0) to better fit estimated seroprevalence.

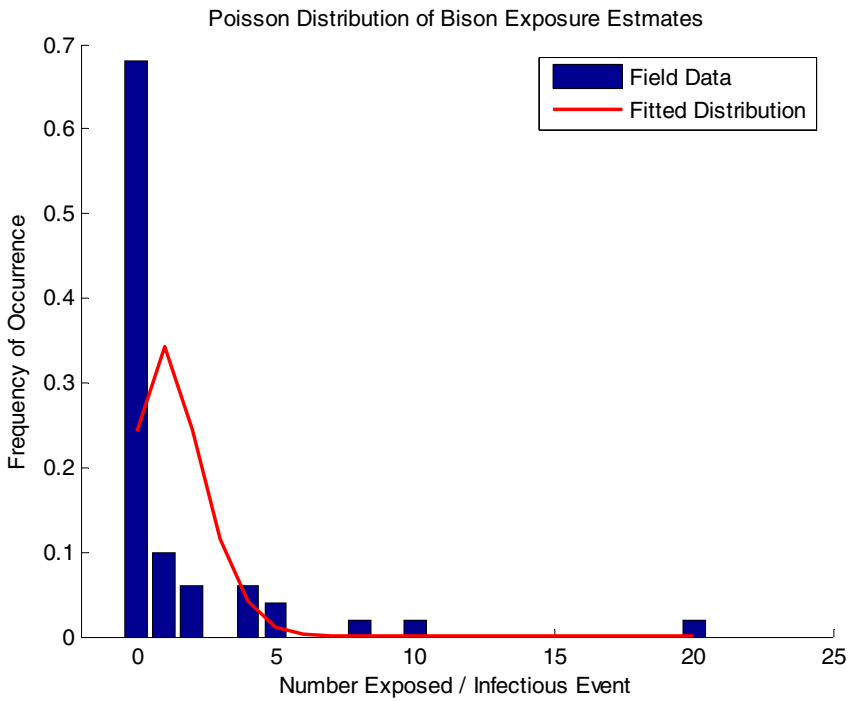


Figure 9. Fitted Poisson distribution to YNP parturition data. Exposures were treated as Poisson random variables and field data was fitted to a Poisson distribution (λ= 1.42).

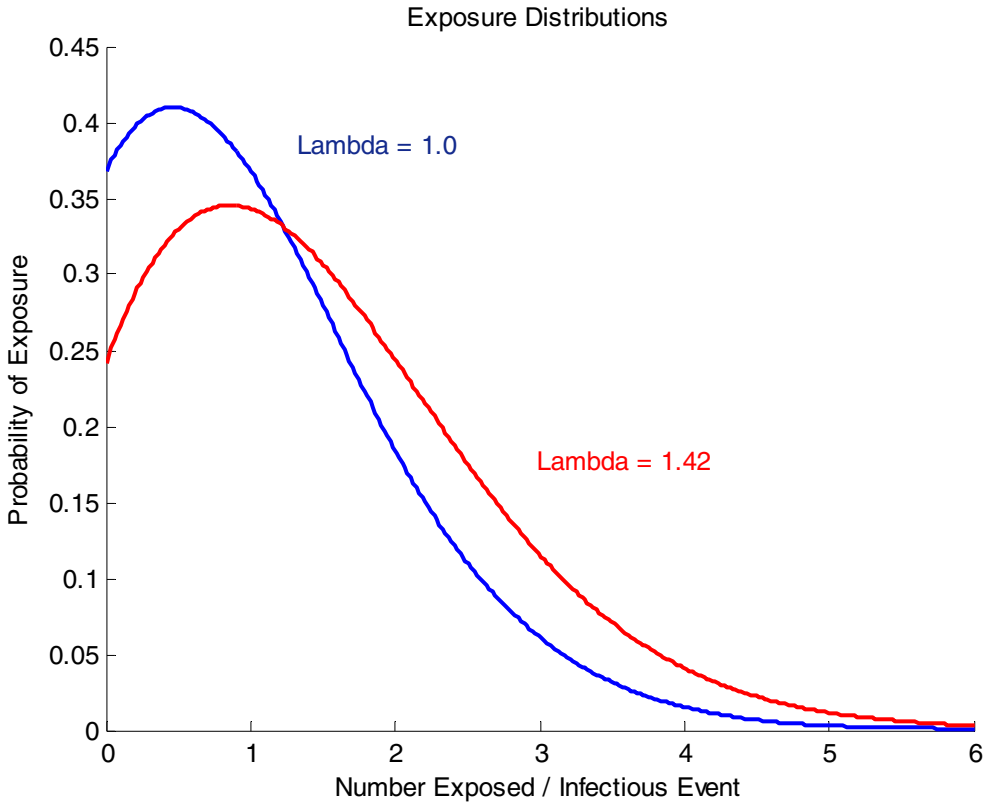


Figure 10. Comparison of distribution from field data (red, λ= 1.42) to adjusted distribution (blue, λ= 1.0). The adjusted distribution fit historical seroprevalence levels (40-60%) and was used in model simulations.

Sensitivity Outputs for Boundary Vaccination of Calves and Yearlings with Various Levels of Vaccine Efficacy

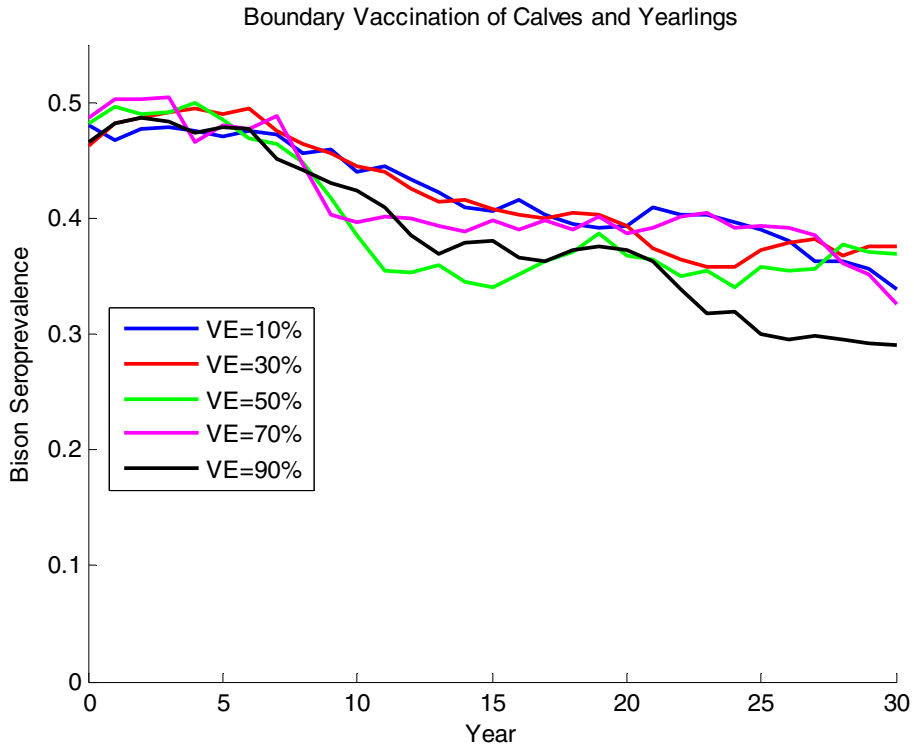


Figure 11a. Simulated seroprevalence declines across a range of vaccine efficacy for alternative A

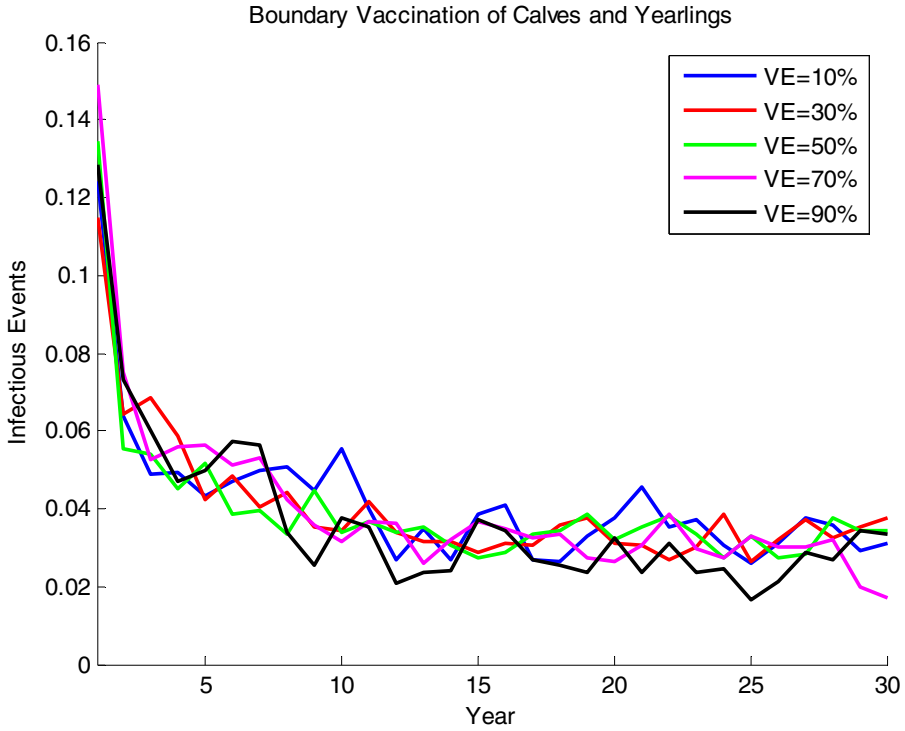


Figure 11b. Simulated declines in infectious events across a range of vaccine efficacy for alternative A

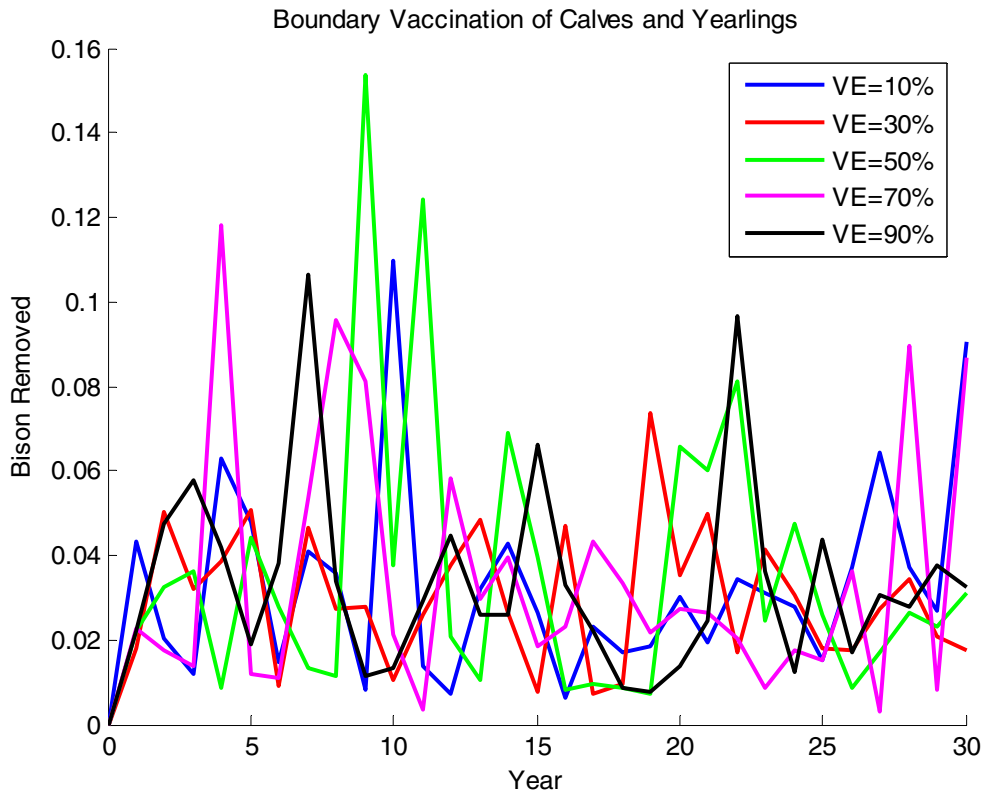


Figure 11c. Simulated boundary removals across a range of vaccine efficacy for alternative A

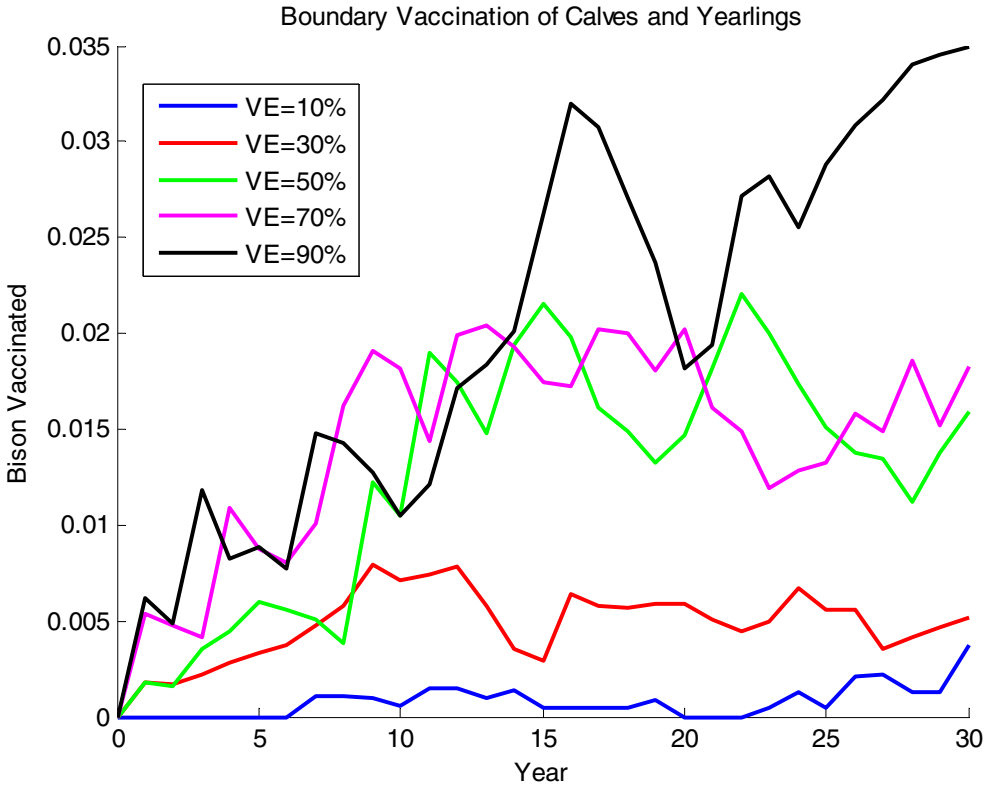


Figure 11d. Simulated proportion of population vaccinated across a range of vaccine efficacy for alternative A

Sensitivity Outputs for Boundary and Remote Vaccination of Calves and Yearlings at different levels of vaccine efficacy (VE)

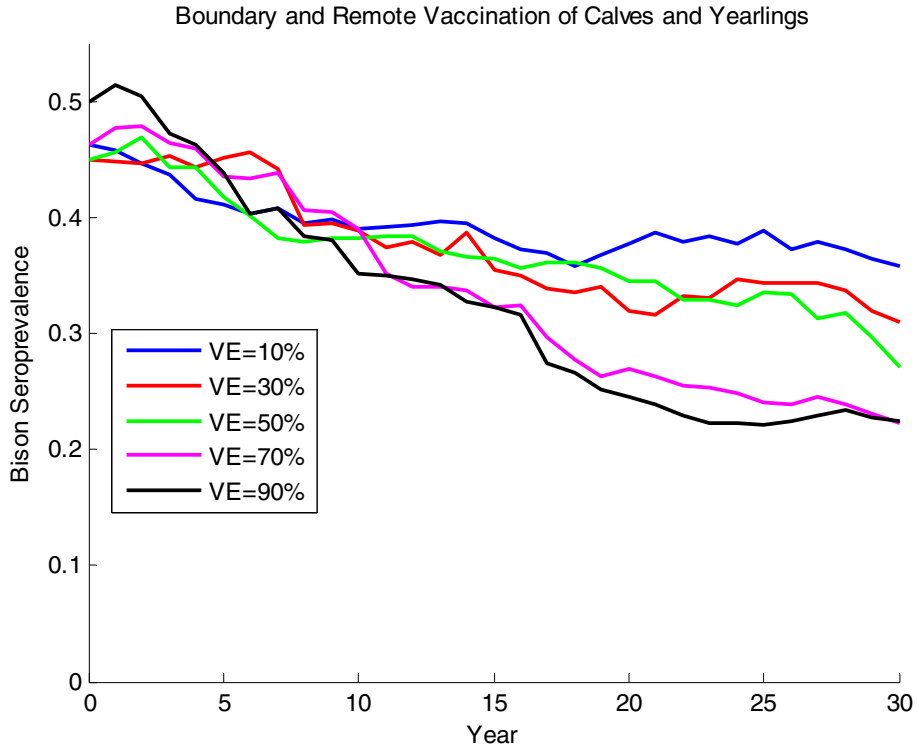


Figure 12a. Simulated seroprevalence declines across a range of vaccine efficacy for alternative B. Remote vaccination effort was held at an intermediate level (.5).

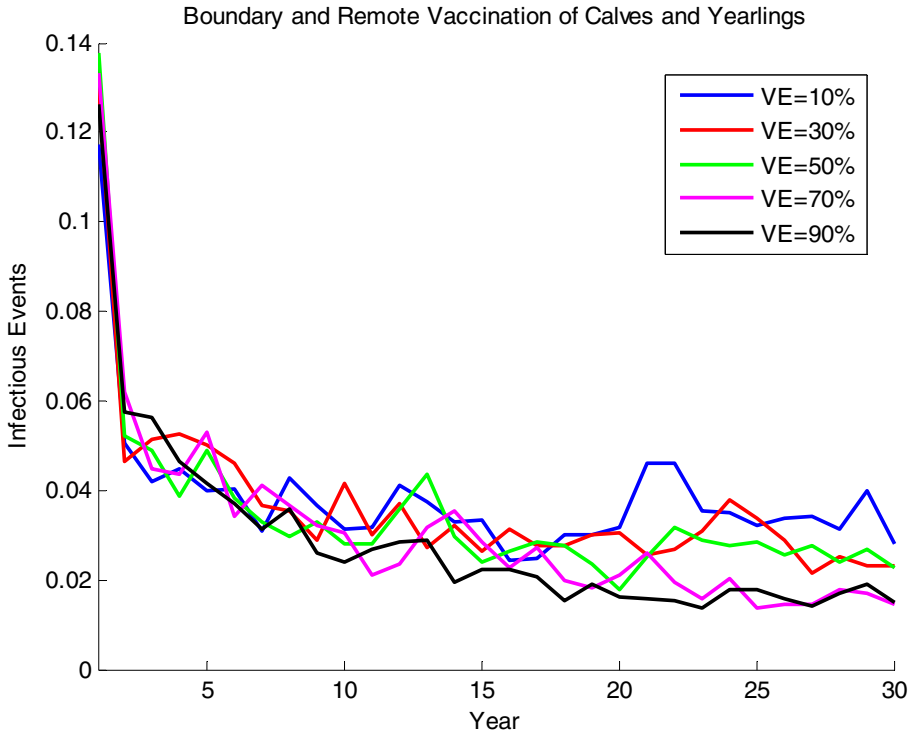


Figure 12b. Simulated declines in infectious events across a range of vaccine efficacy for alternative B. Remote vaccination effort was held at an intermediate level (.5).

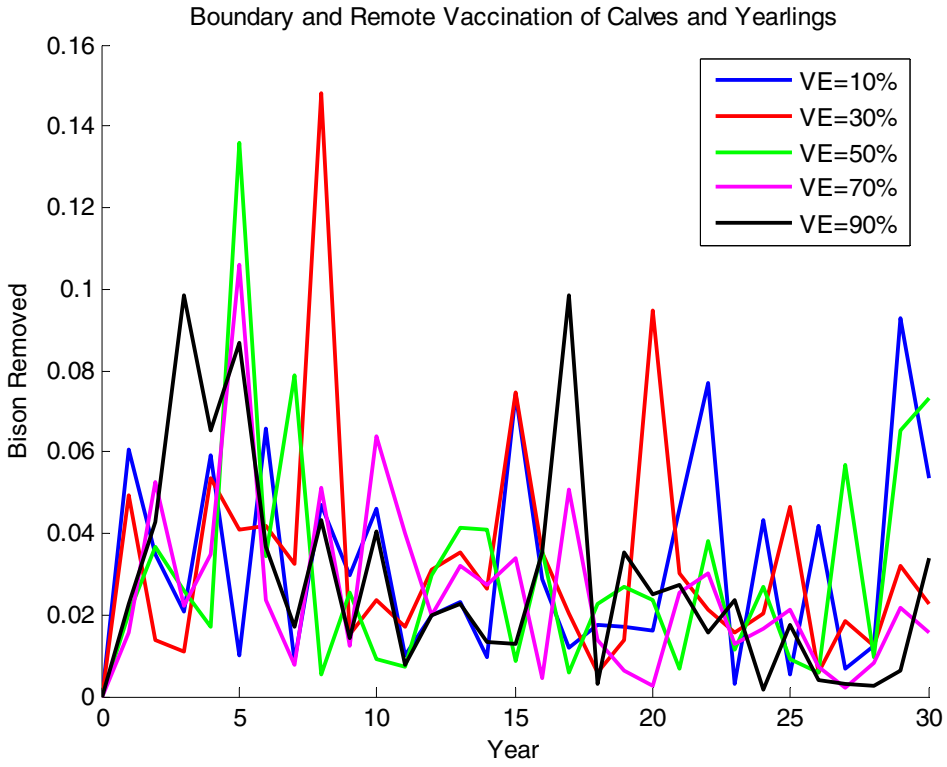


Figure 12c. Simulated boundary removals across a range of vaccine efficacy for alternative B. Remote vaccination effort was held at an intermediate level (.5).

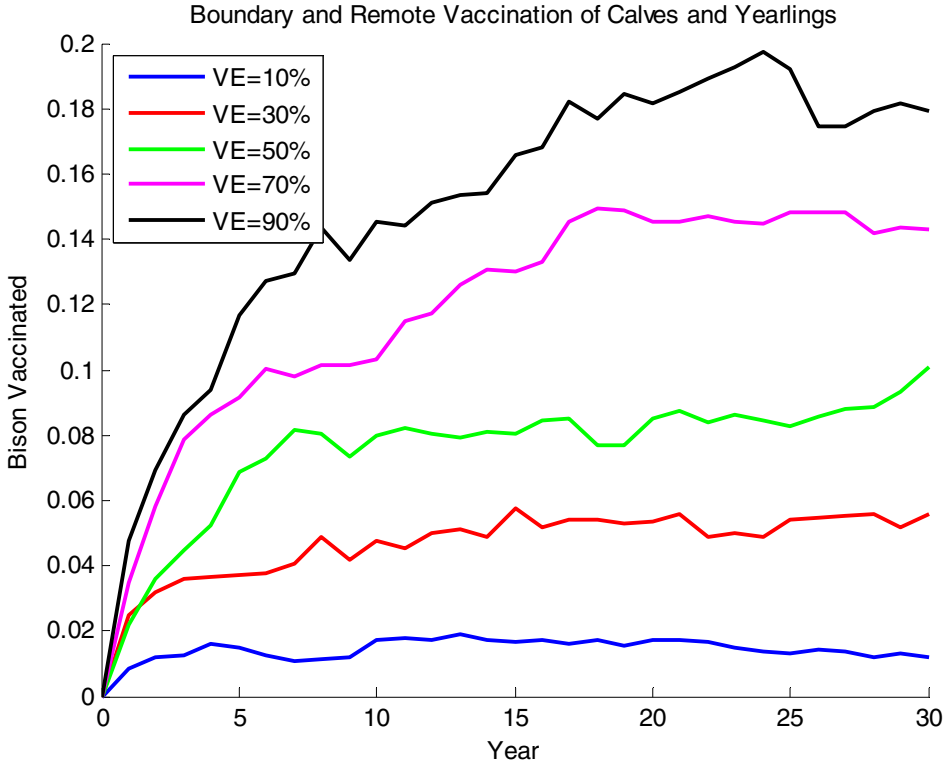


Figure 12d. Simulated proportion of population vaccinated across a range of vaccine efficacy for alternative B. Remote vaccination effort was held at an intermediate level (.5).

Sensitivity Outputs for Boundary and Remote Vaccination of All Female Bison at different levels of vaccine efficacy (VE)

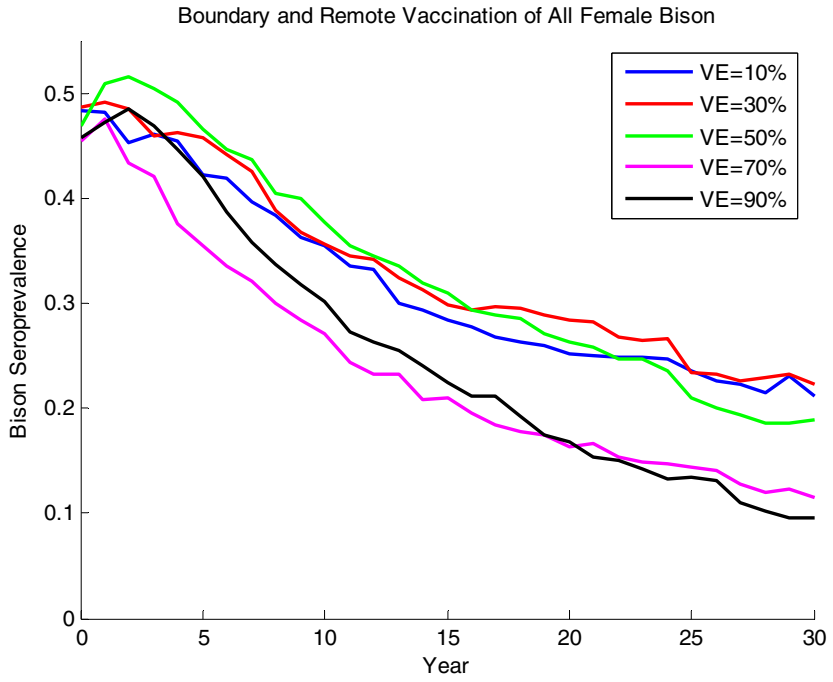


Figure 13a. Simulated seroprevalence declines across a range of vaccine efficacy for alternative C. Remote vaccination effort was held at an intermediate level (.5).

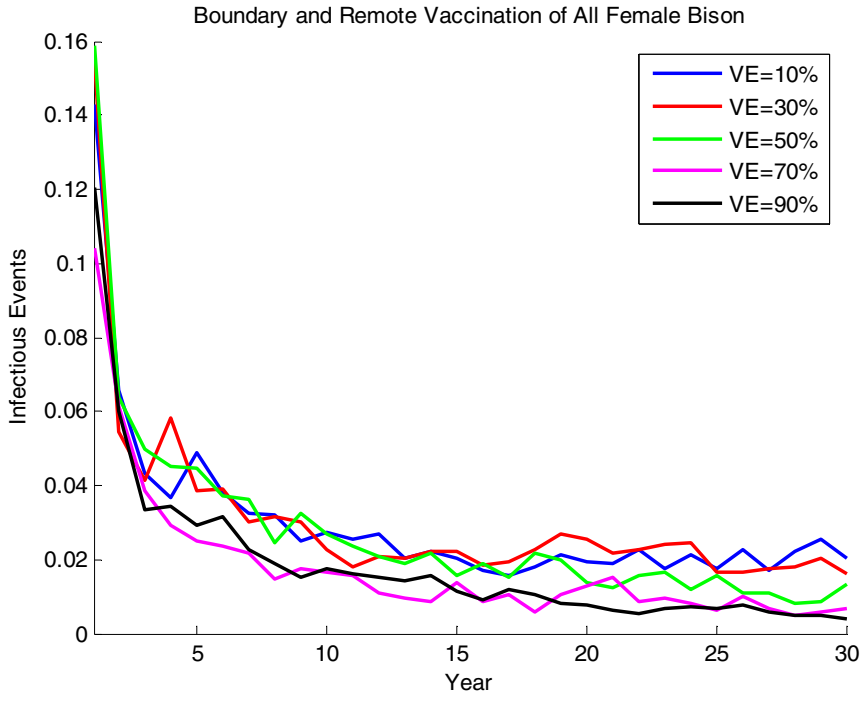


Figure 13b. Simulated declines in infectious events across a range of vaccine efficacy for alternative C. Remote vaccination effort was held at an intermediate level (.5).

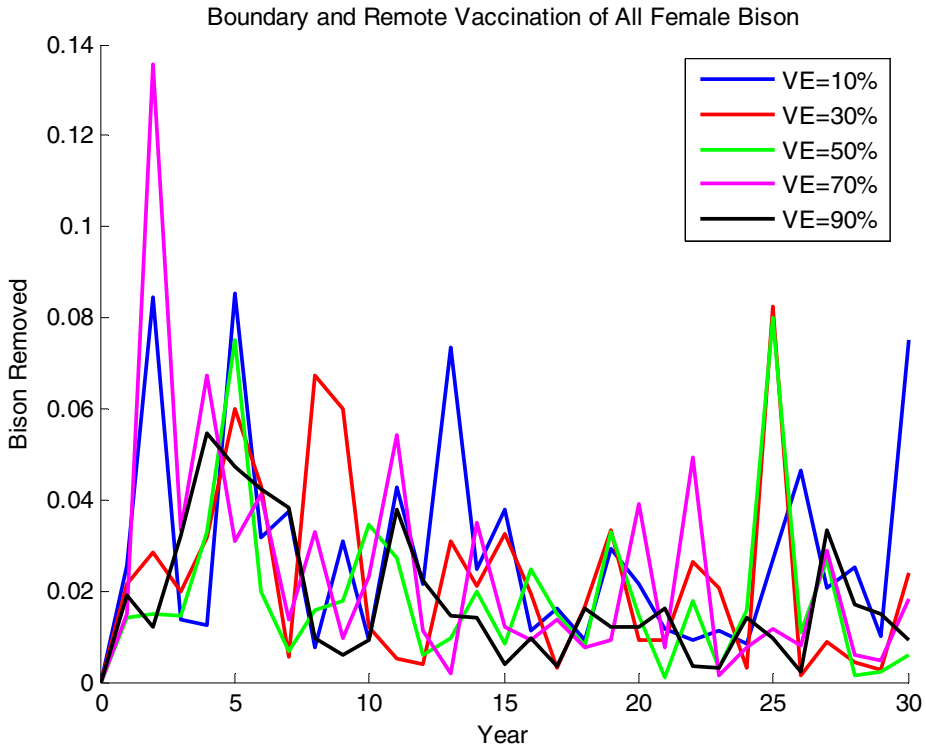


Figure 13c. Simulated boundary removals across a range of vaccine efficacy for alternative C. Remote vaccination effort was held at an intermediate level (.5).

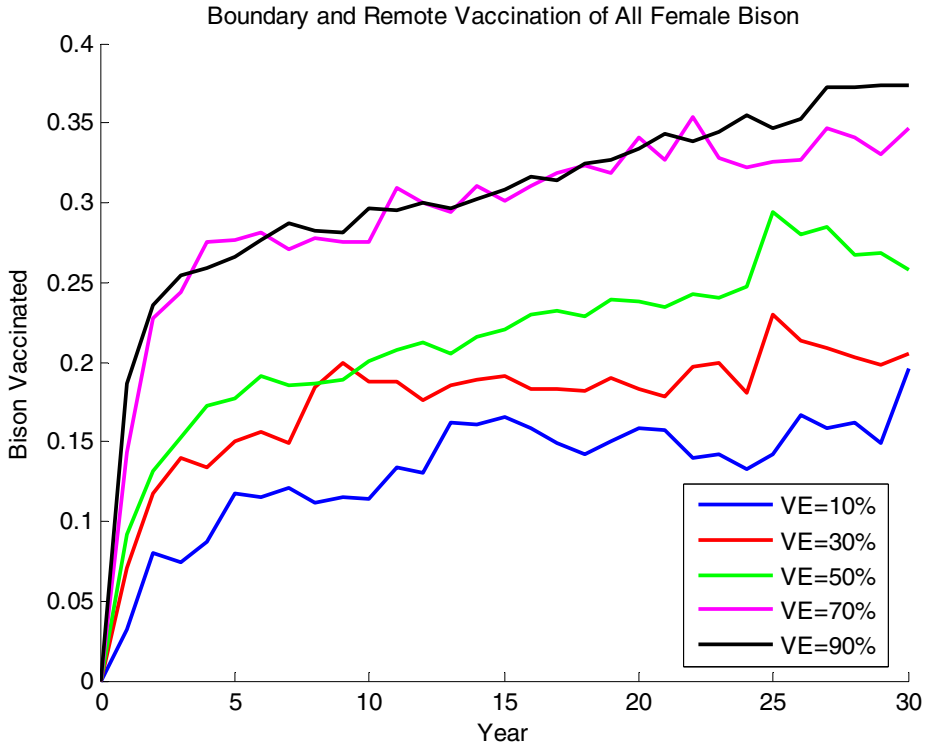


Figure 13d. Simulated proportion of population vaccinated across a range of vaccine efficacy for alternative C. Remote vaccination effort was held at an intermediate level (.5).

Simulations of Management Alternatives

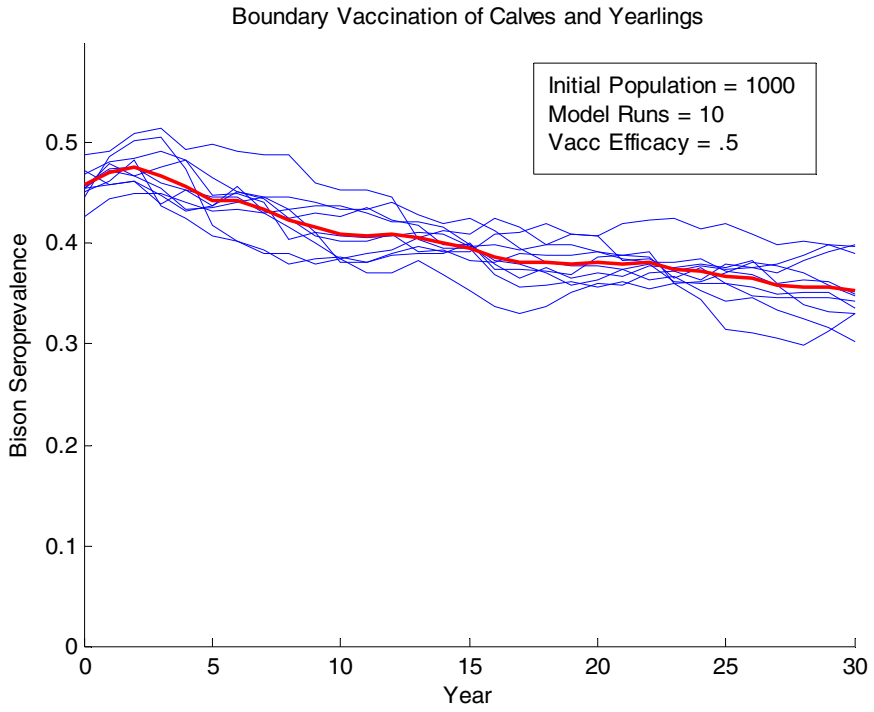


Figure 14a. Results of 10 simulations of seroprevalence decline corresponding to boundary vaccination of calves and yearlings captured during management actions outside the park. The red line represents the mean value of the 10 simulations.

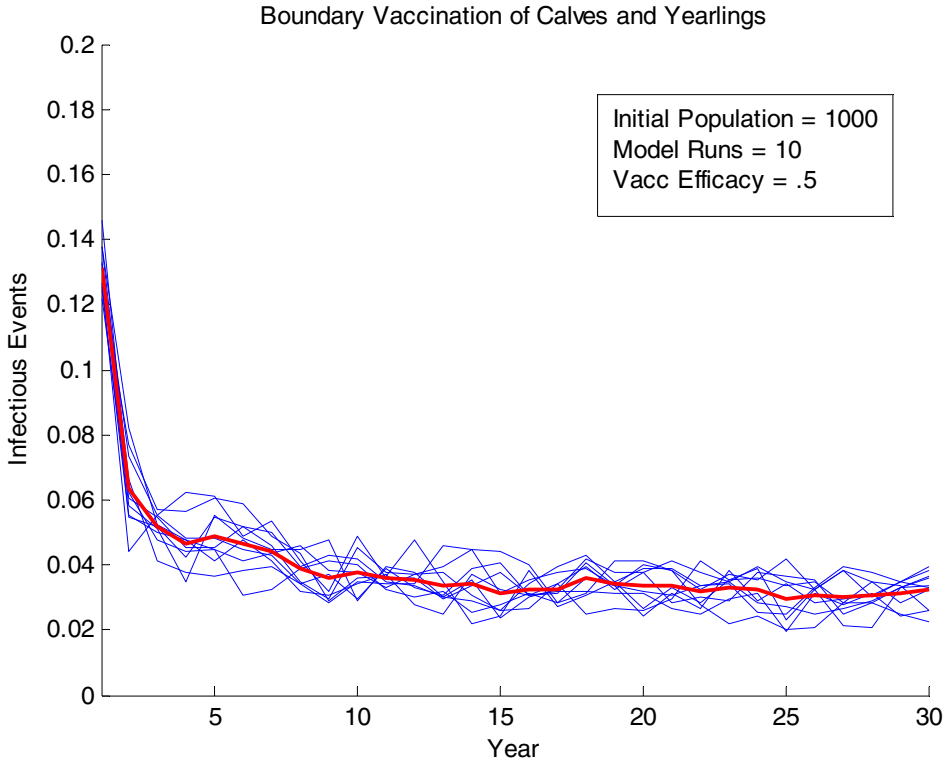


Figure 14b. Results of 10 simulations corresponding to the proportion of infectious events (abortions and live births) associated with boundary vaccination of calves and yearlings captured during management actions outside the park. The red line represents the mean value of the 10 simulations.

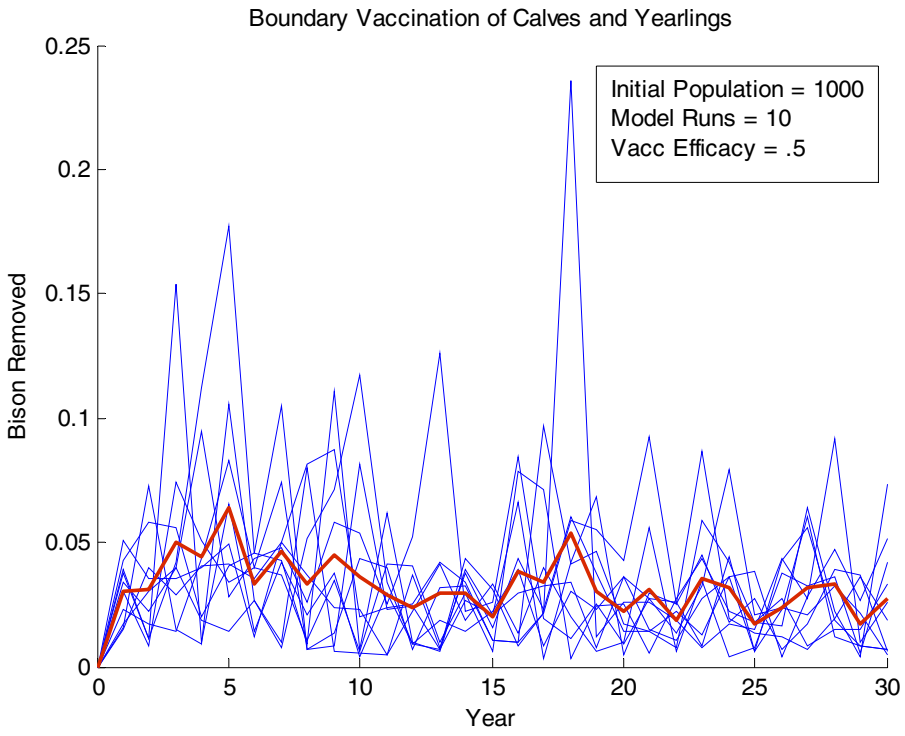


Figure 14c. Results of 10 simulations corresponding to the proportion of seropositive bison detected and removed during boundary vaccination of calves and yearlings outside the park. The red line represents the mean value of the 10 simulations.

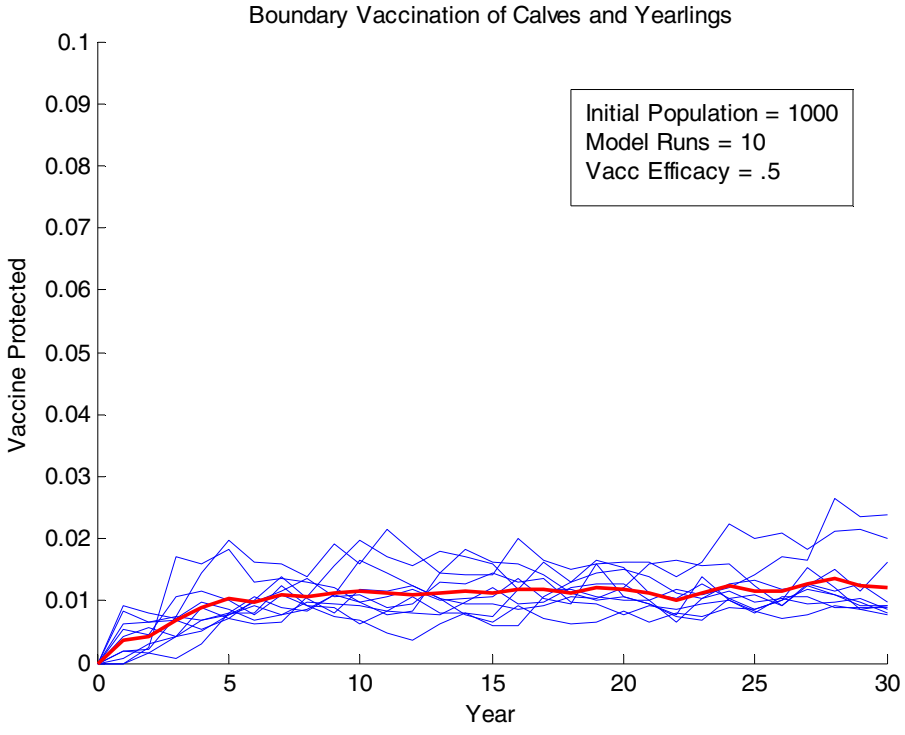


Figure 14d. Results of 10 simulations corresponding to the proportion of bison vaccinated with boundary vaccination of calves and yearlings captured during management actions outside the park. The red line represents the mean value of the 10 simulations.

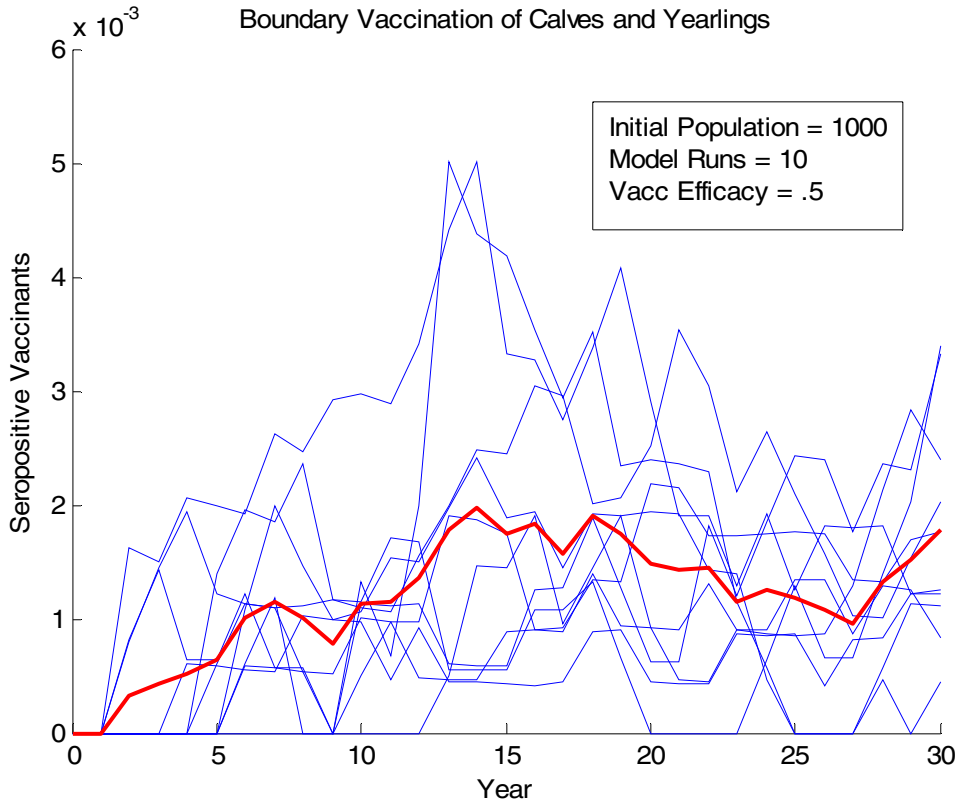


Figure 14e. Results of 10 simulations corresponding to the proportion of bison vaccinated that have been subsequently exposed to field strain *Brucella*. These bison are protected from shedding the bacteria, but will react positively on serologic tests. Simulations correspond to boundary vaccination of calves and yearlings captured during management actions outside the park. The red line represents the mean value of the 10 simulations.

ALTERNATIVE B

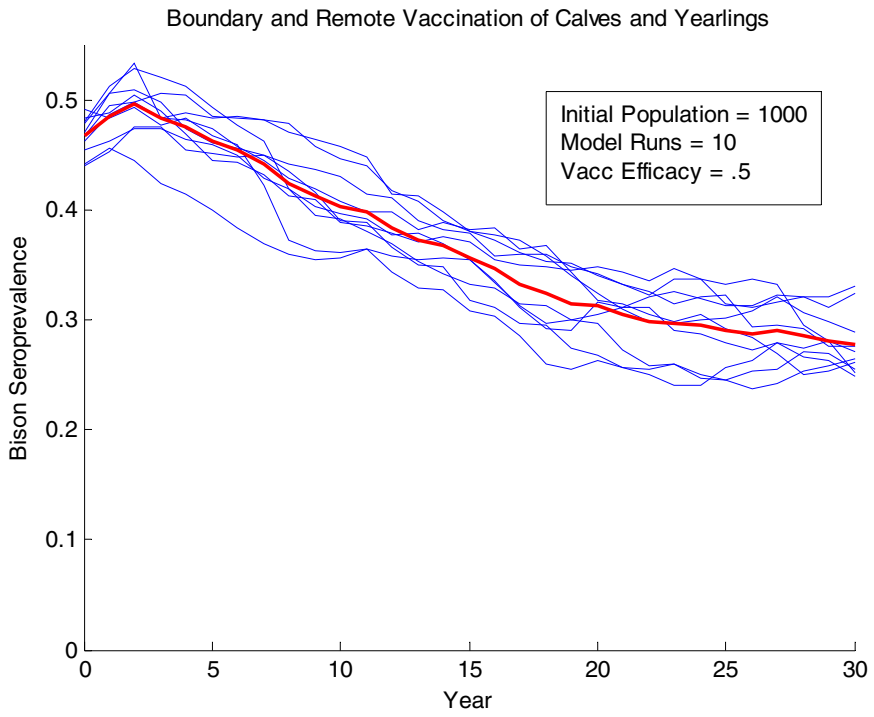


Figure 15a. Results of 10 simulations of seroprevalence decline corresponding to boundary and remote vaccination of calves and yearlings. The red line represents the mean value of the 10 simulations.

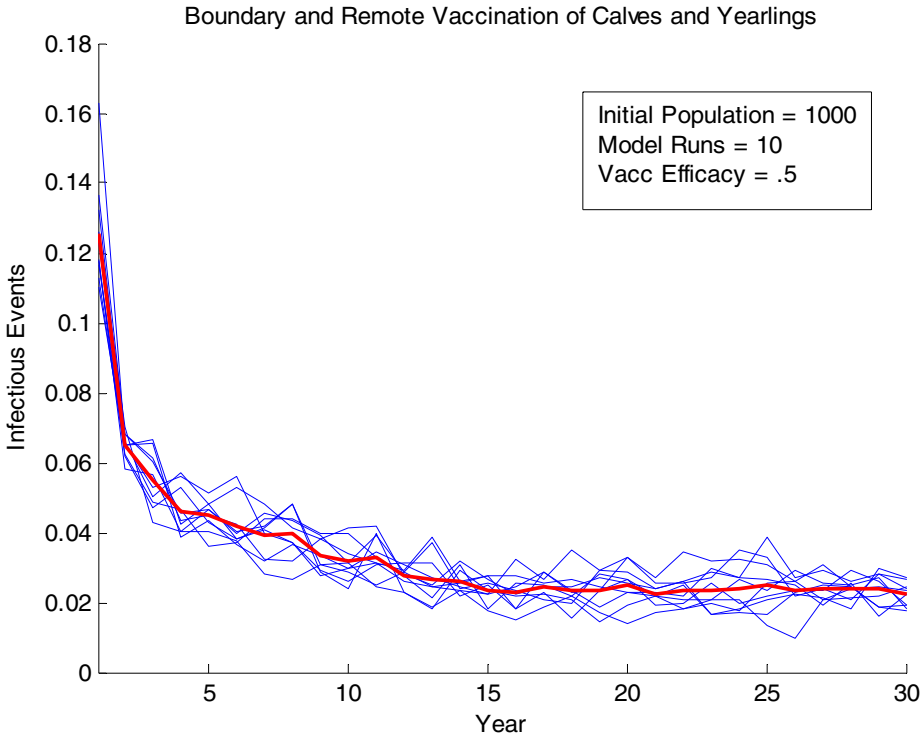


Figure 15b. Results of 10 simulations corresponding to the proportion of infectious events (abortions and live births) associated with boundary and remote vaccination of calves and yearlings. The red line represents the mean value of the 10 simulations.

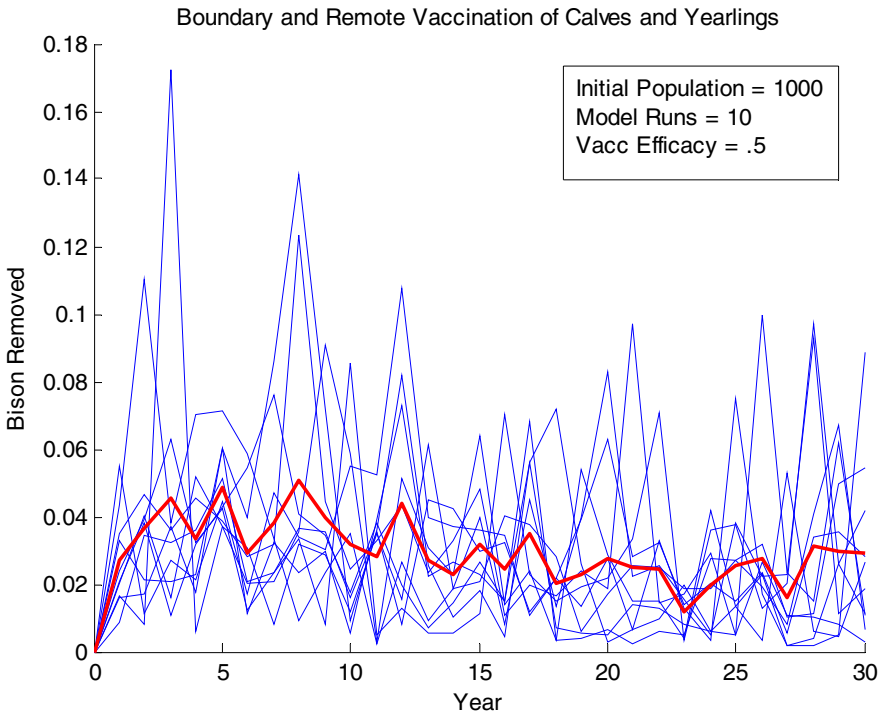
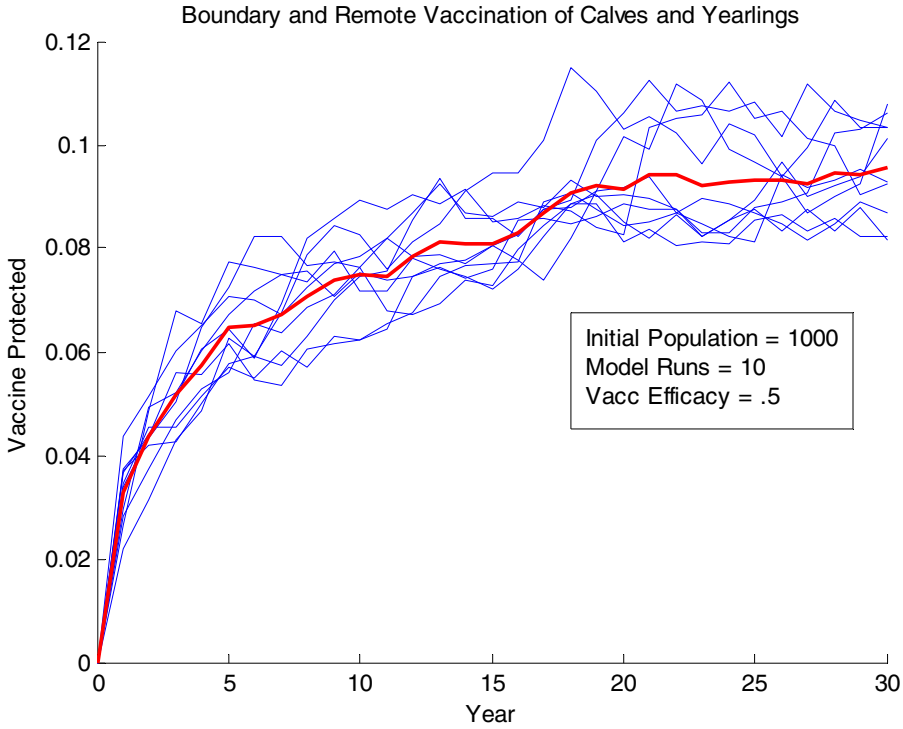


Figure 15c. Results of 10 simulations corresponding to the proportion of seropositive bison detected and removed during boundary vaccination of alternative B. The red line represents the mean value of the 10 simulations.



Figured 15d. Results of 10 simulations corresponding to the proportion of the bison population vaccinated with boundary and remote vaccination of calves and yearlings. The red line represents the mean value of the 10 simulations.

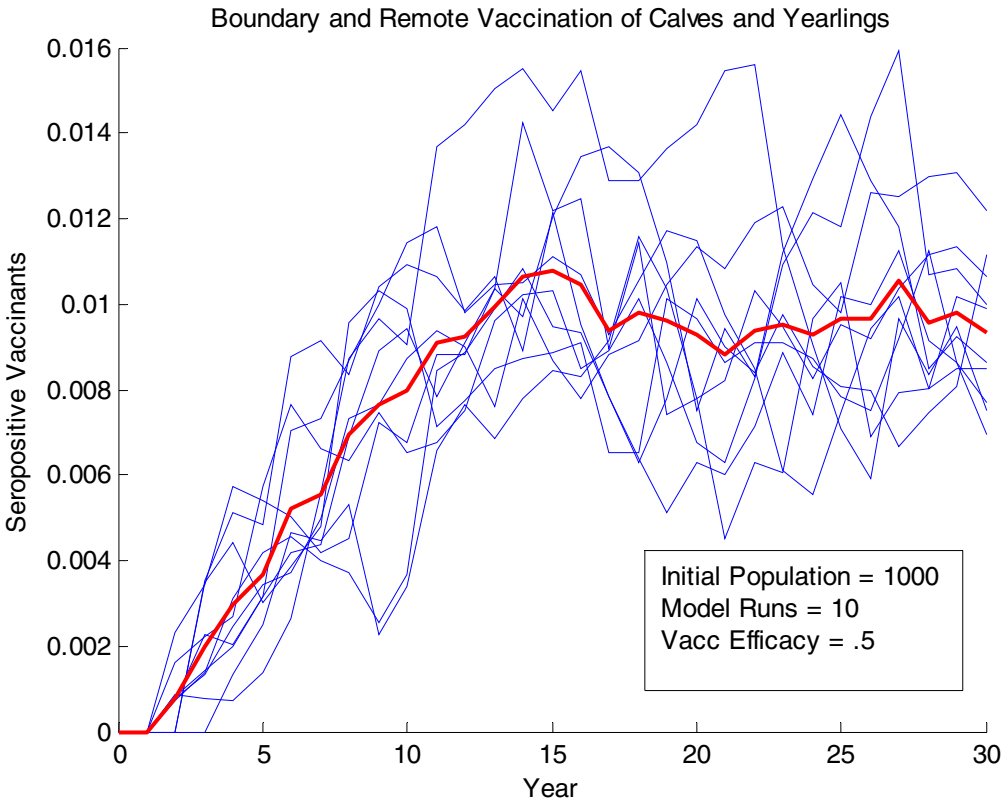


Figure 15e. Results of 10 simulations corresponding to the proportion of bison vaccinated that have been subsequently exposed to field strain *Brucella*. These bison are protected from shedding the bacteria, but will react positively on serologic tests. Simulations correspond to boundary and remote vaccination of calves and yearlings captured during management actions outside the park. The red line represents the mean value of the 10 simulations.

ALTERNATIVE C

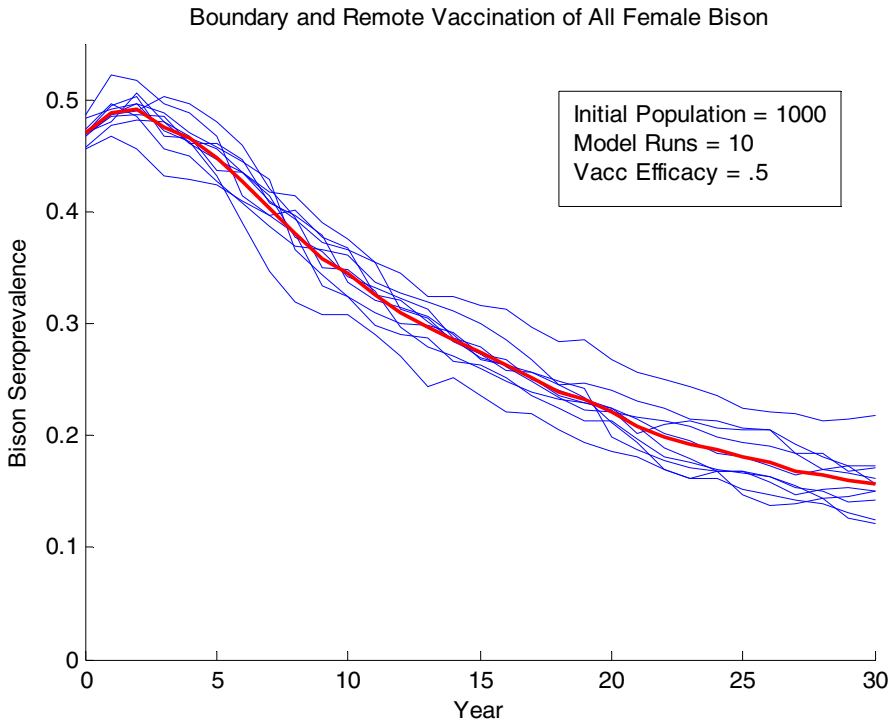


Figure 16a. Results of 10 simulations of seroprevalence decline corresponding to boundary and remote vaccination of all female bison. The red line represents the mean value of the 10 simulations

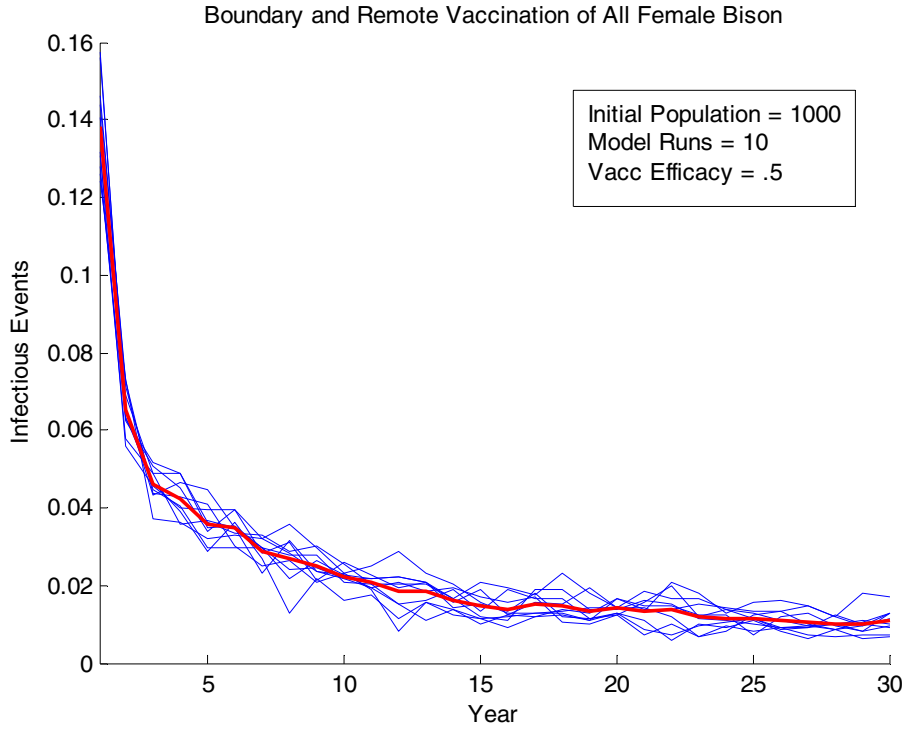


Figure 16b. Results of 10 simulations corresponding to the proportion of infectious events (abortions and live births) associated with boundary and remote vaccination of all female bison. The red line represents the mean value of the 10 simulations.

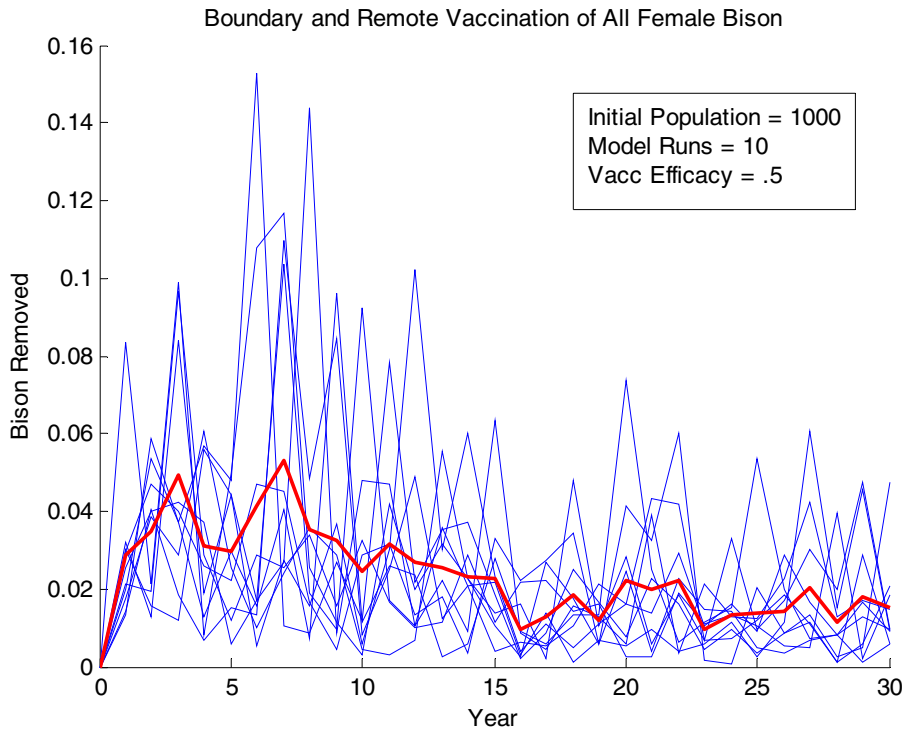
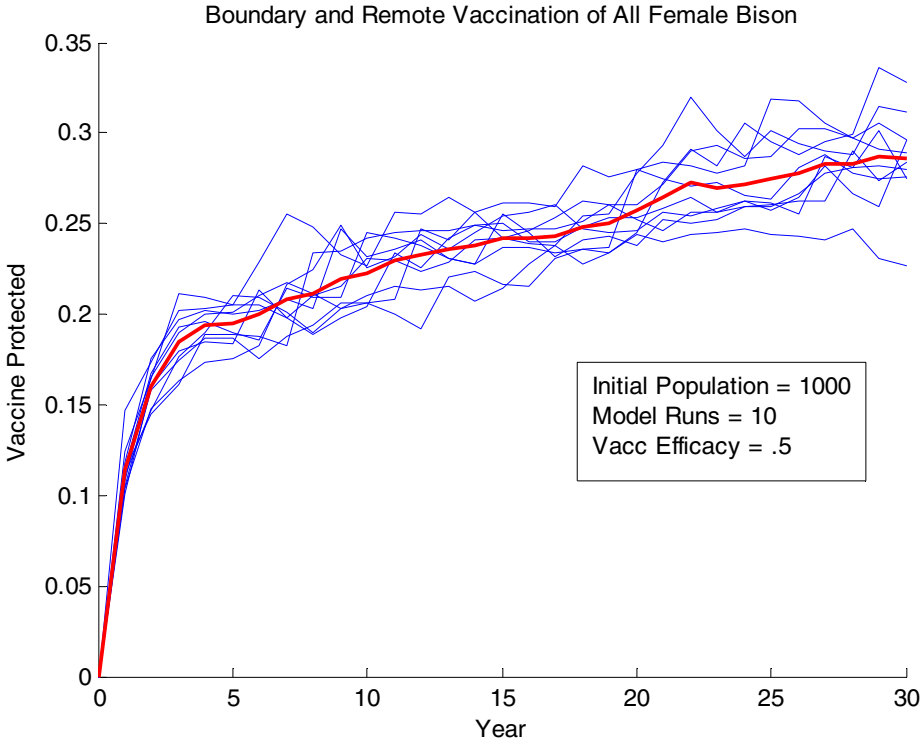


Figure 16c. Results of 10 simulations corresponding to the proportion of seropositive bison detected and removed during boundary vaccination of alternative C. The red line represents the mean value of the 10 simulations.



Figured 16d. Results of 10 simulations corresponding to the proportion of the bison population vaccinated with boundary and remote vaccination of all female bison. The red line represents the mean value of the 10 simulations

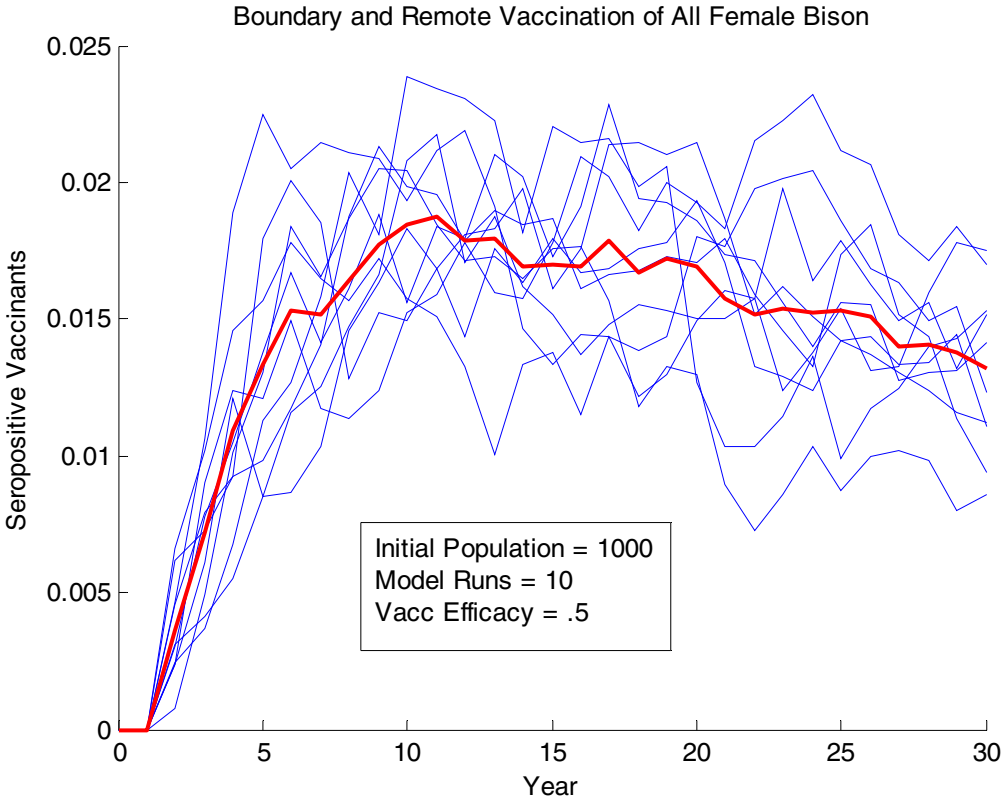


Figure 16e . Results of 10 simulations corresponding to the proportion of bison vaccinated that have been subsequently exposed to field strain *Brucella*. These bison are protected from shedding the bacteria, but will react positively on serologic tests. Simulations correspond to boundary and remote vaccination of all female bison. The red line represents the mean value of the 10 simulations.

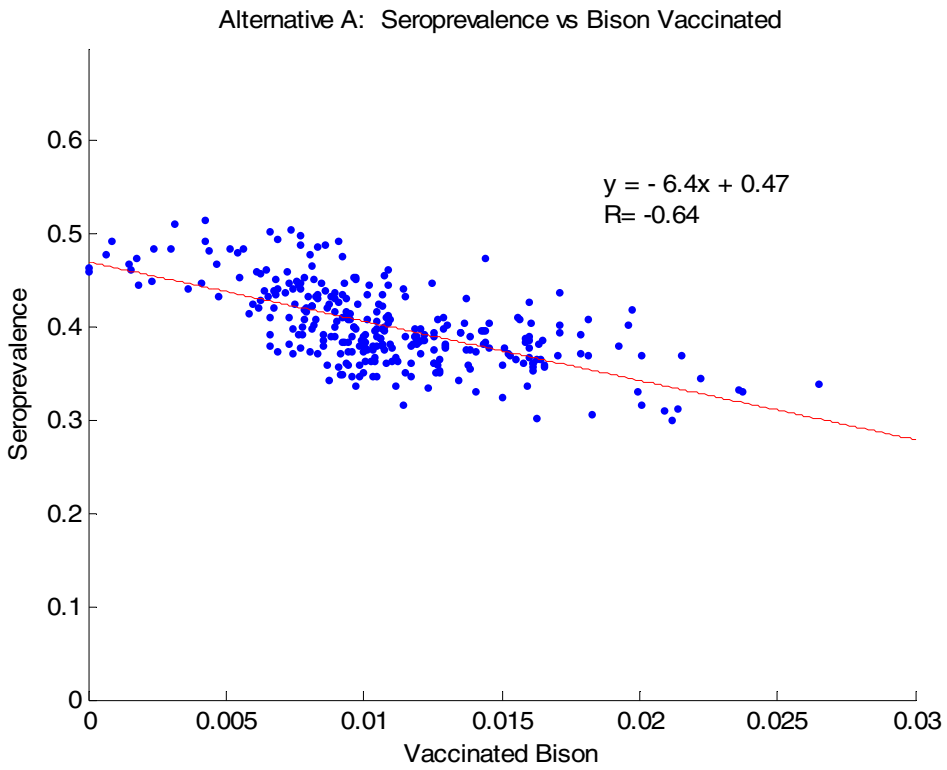


Figure 17a. Relationship between seroprevalence and proportion of bison population vaccinated in the 30 year period modeled. Trend line is for reference and not to be interpreted beyond plotted data.

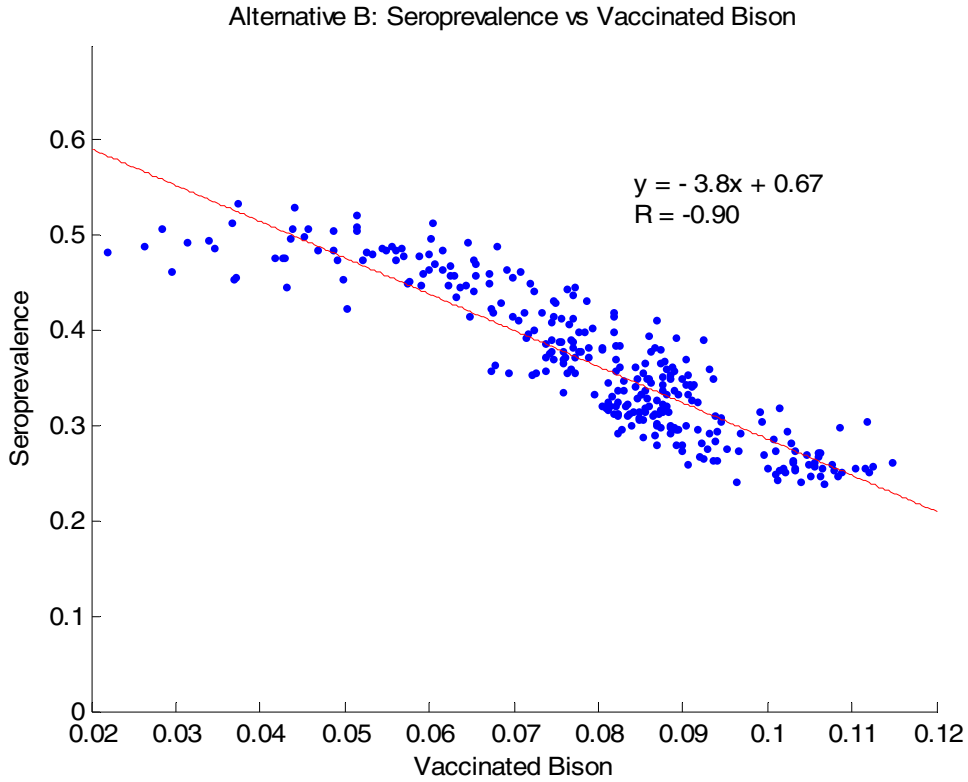


Figure 17b. Relationship between seroprevalence and proportion of bison population vaccinated in the 30 year period modeled. Trend line is for reference and not to be interpreted beyond plotted data.

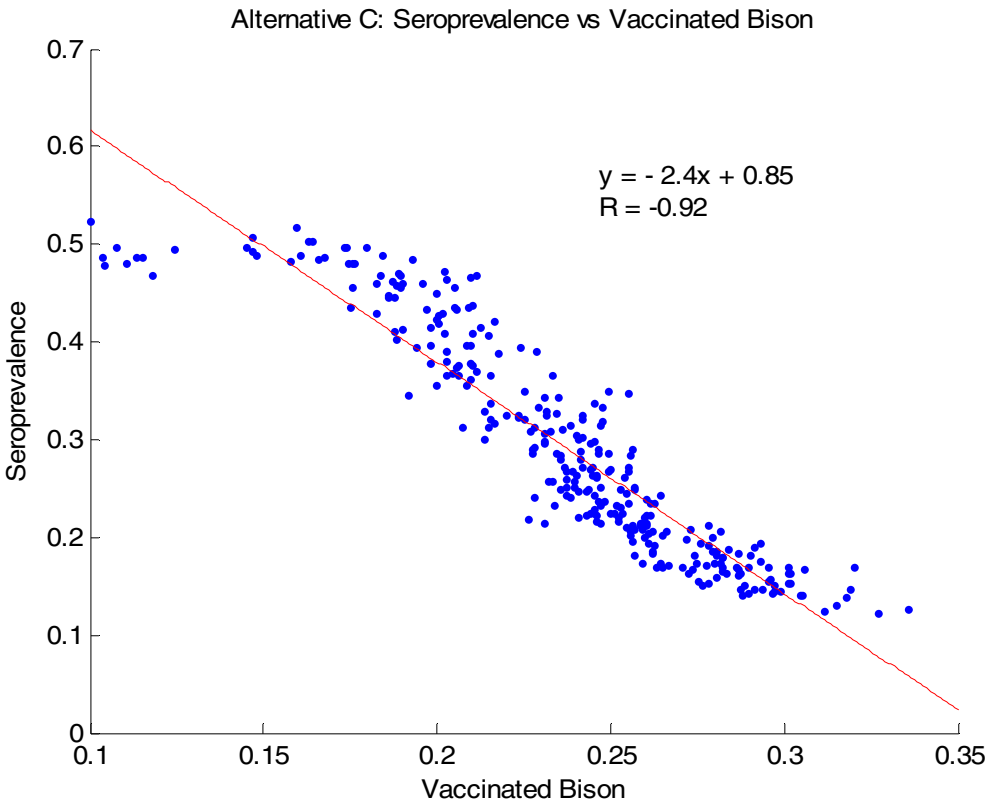


Figure 17c. Relationship between seroprevalence and proportion of bison population vaccinated in the 30 year period modeled. Trend line is for reference and not to be interpreted beyond plotted data.

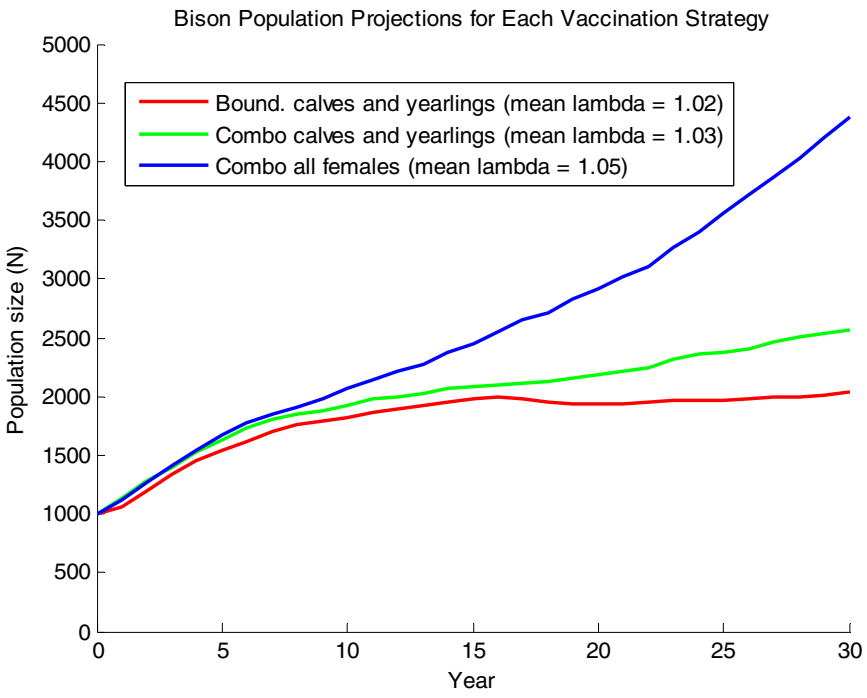


Figure 18. Simulated growth of the bison population under each management alternative. Lambda values represent mean values of annual growth over the 30 year period modeled.

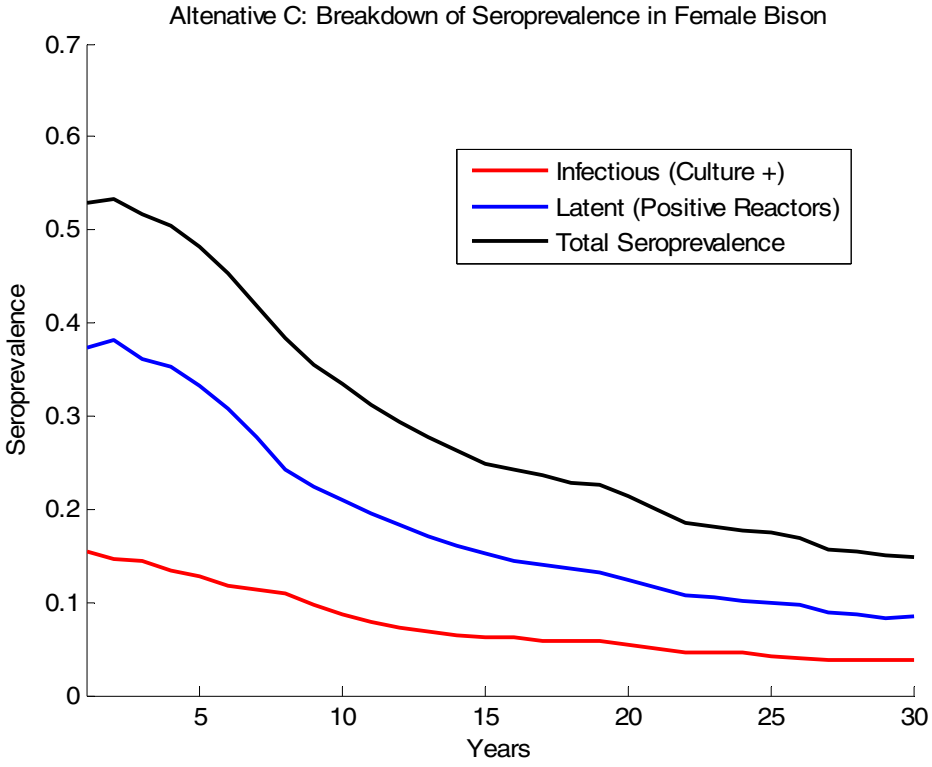


Figure 19. Breakdown of seroprevalence under alternative C. Population seroprevalence (black) is comprised of both infectious (I) and Latent (L) bison. Seroprevalence rates are likely to be much higher than the level of active infection. Monitoring declines in seroprevalence alone may not reflect the declining level of brucellosis infection.

Declining Duration of Protection

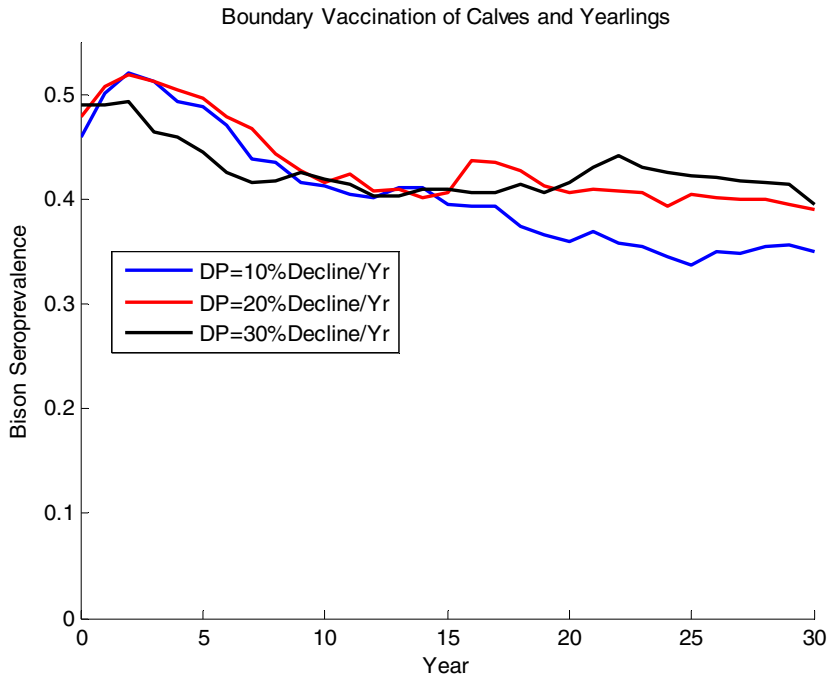


Figure 20a. Simulation of seroprevalence decline at different levels of duration of vaccine protection for alternative A. The level of vaccine protection (efficacy) declined by the specified proportion per year.

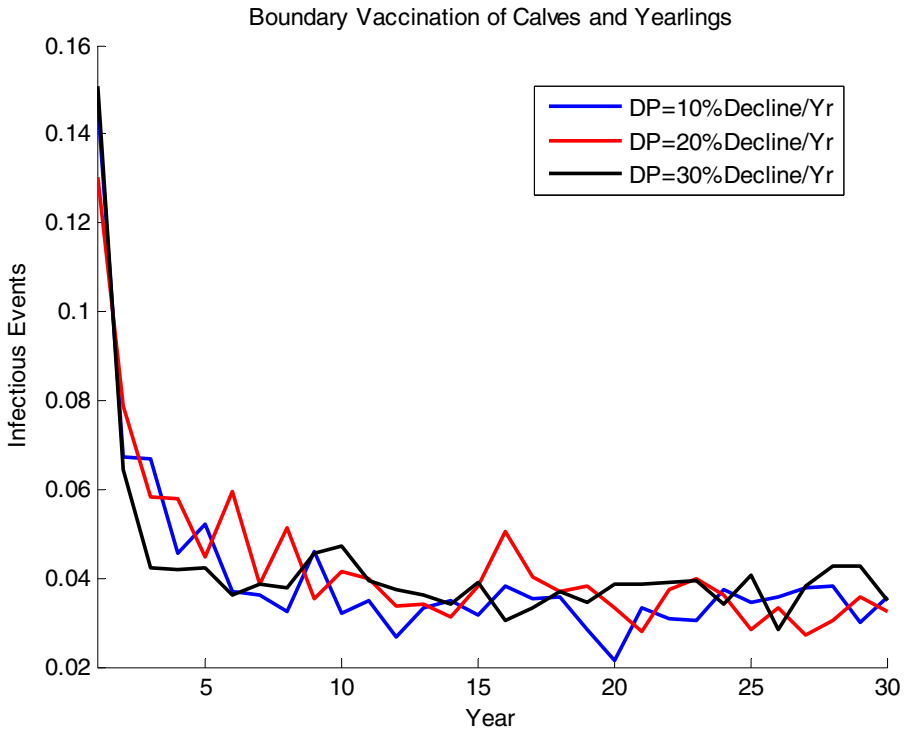


Figure 20b. Simulation of the decline in infectious events at different levels of duration of vaccine protection for alternative A. The level of vaccine protection (efficacy) declined by the specified proportion per year.

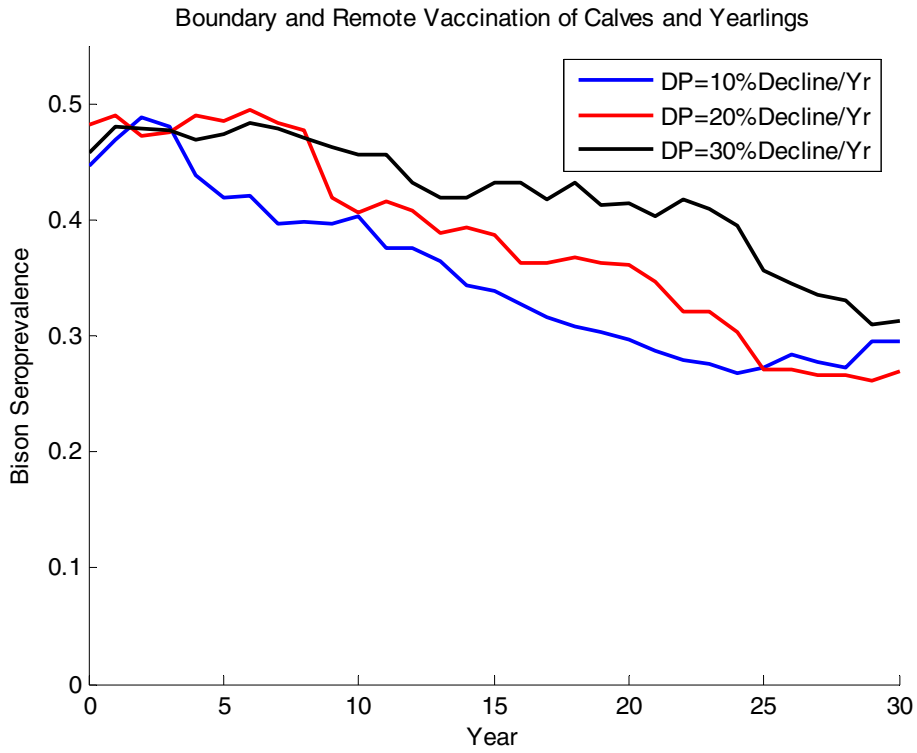


Figure 21a. Simulation of seroprevalence decline at different levels of duration of vaccine protection for alternative B. The level of vaccine protection (efficacy) declined by the specified proportion per year.

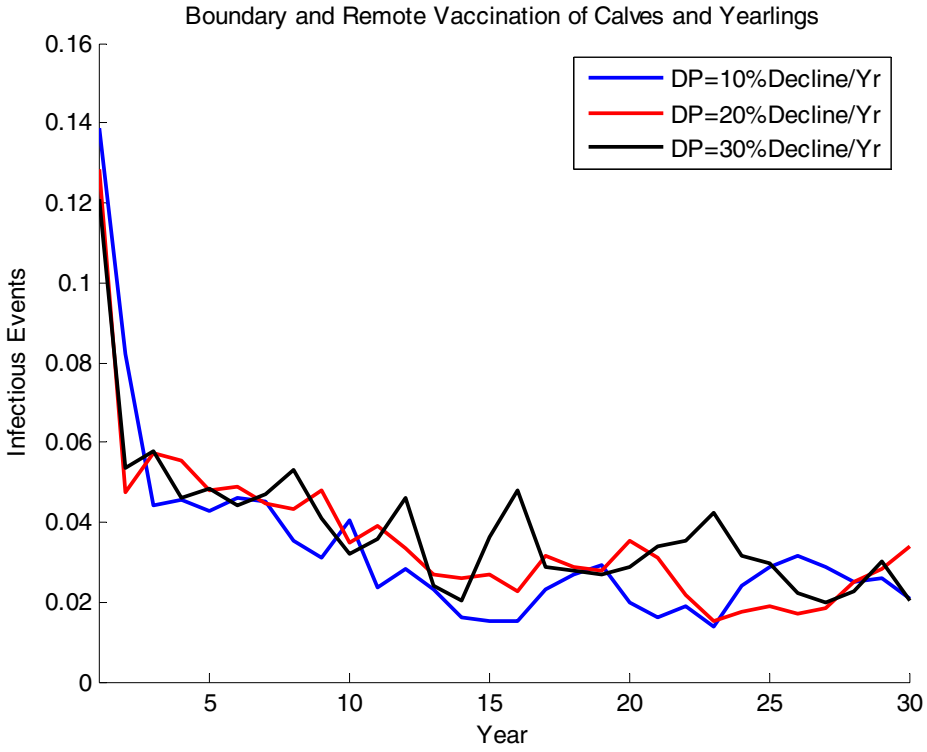


Figure 21b. Simulation of the decline in infectious events at different levels of duration of vaccine protection for alternative A. The level of vaccine protection (efficacy) declined by the specified proportion per year.

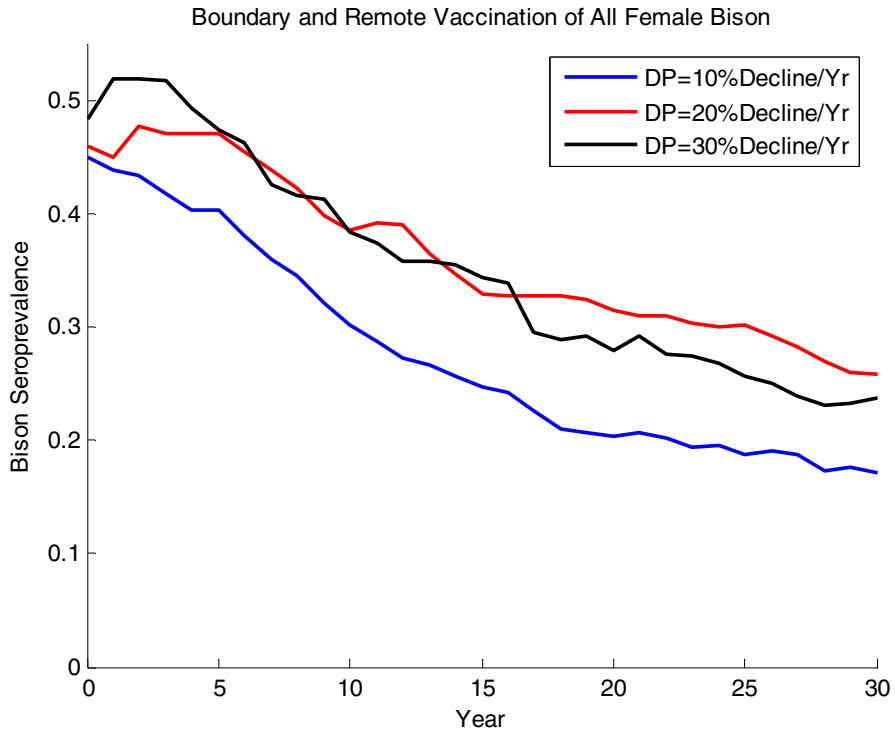


Figure 22a. Simulation of seroprevalence decline at different levels of duration of vaccine protection for alternative A. The level of vaccine protection (efficacy) declined by the specified proportion per year.

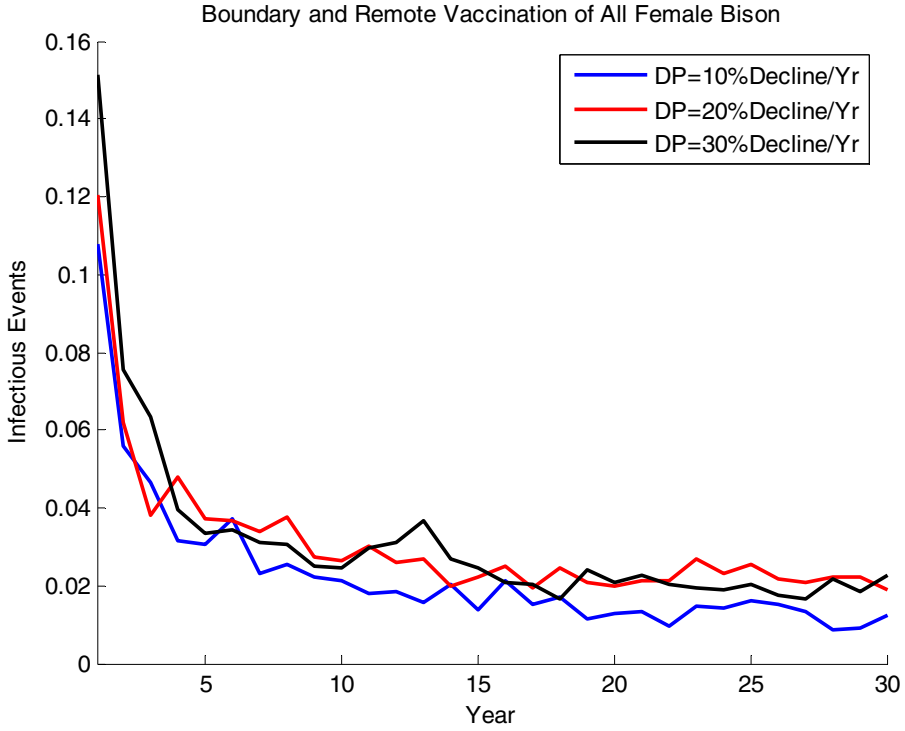


Figure 22b. Simulation of the decline in infectious events at different levels of duration of vaccine protection for alternative A. The level of vaccine protection (efficacy) declined by the specified proportion per year.

Model Simulations Comparing Short-term (10 Years) Vaccination between Alternative A and C

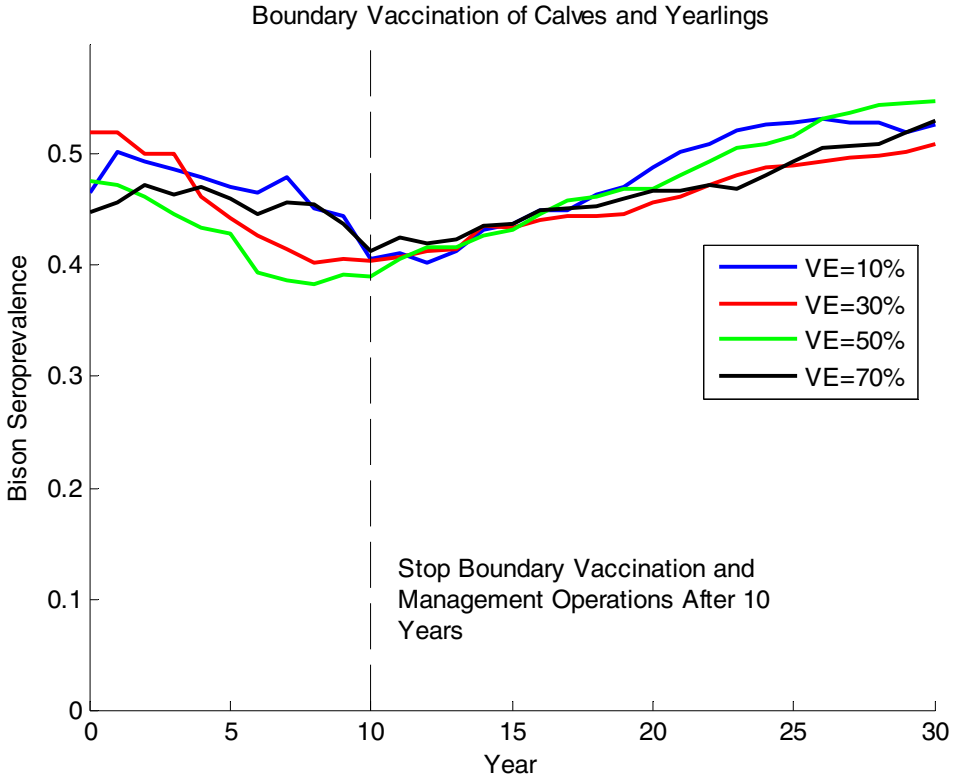


Figure 23a. Simulated seroprevalence decline and increase corresponding to short-term vaccination (10 years) under alternative A. Simulations were run at specified levels of vaccine efficacy.

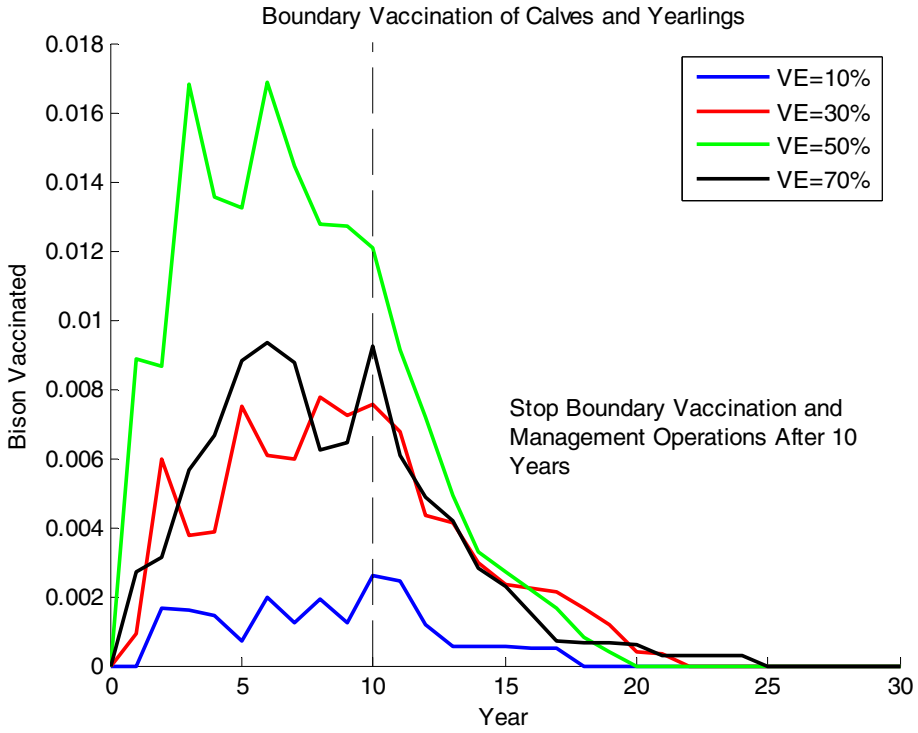


Figure 23b. Simulated increase and decrease of bison vaccinated corresponding to short-term vaccination (10 years) under alternative A. Simulations were run at specified levels of vaccine efficacy.

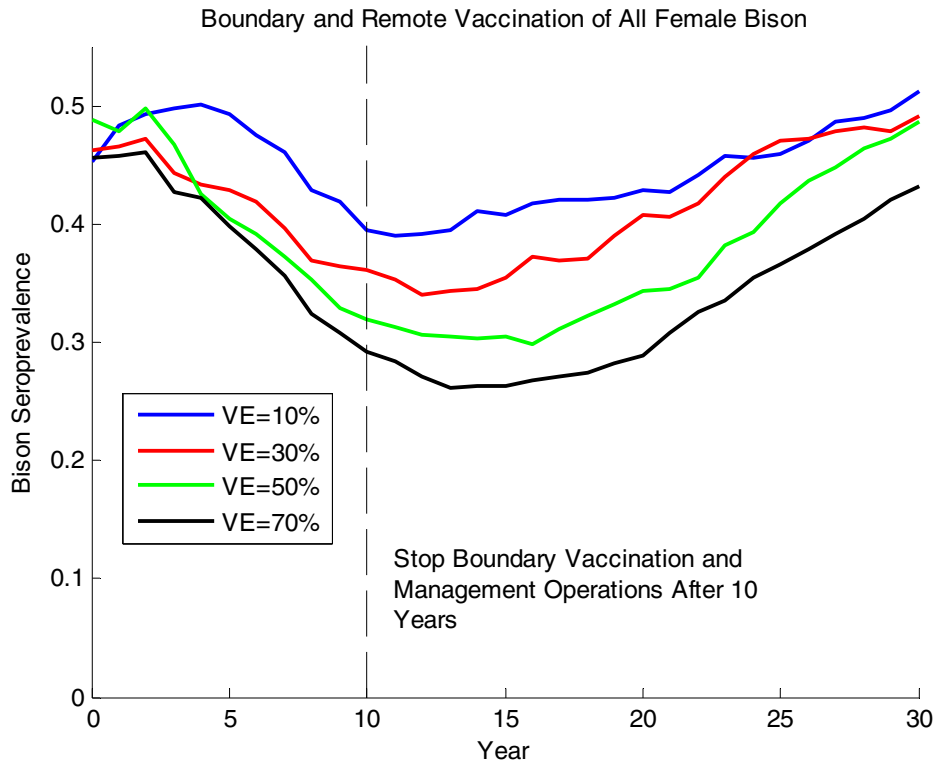


Figure 24a. Simulated seroprevalence decline and increase corresponding to short-term vaccination (10 years) under alternative C. Simulations were run at specified levels of vaccine efficacy.

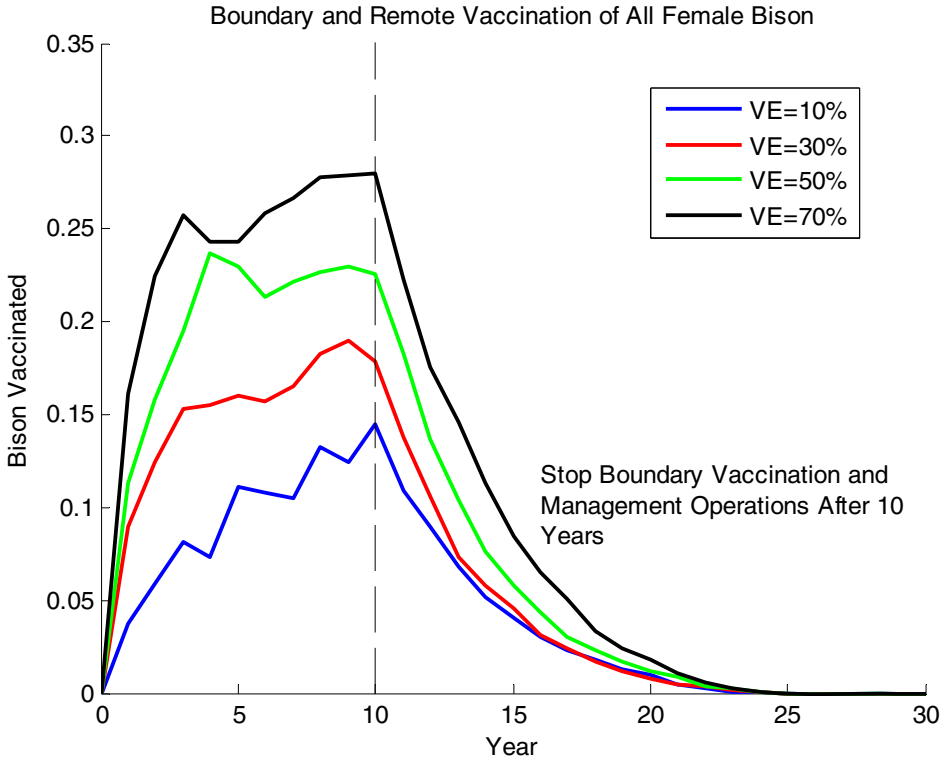


Figure 24b. Simulated increase and decrease of bison vaccinated corresponding to short-term vaccination (10 years) under alternative A. Simulations were run at specified levels of vaccine efficacy.

Summary Graphics

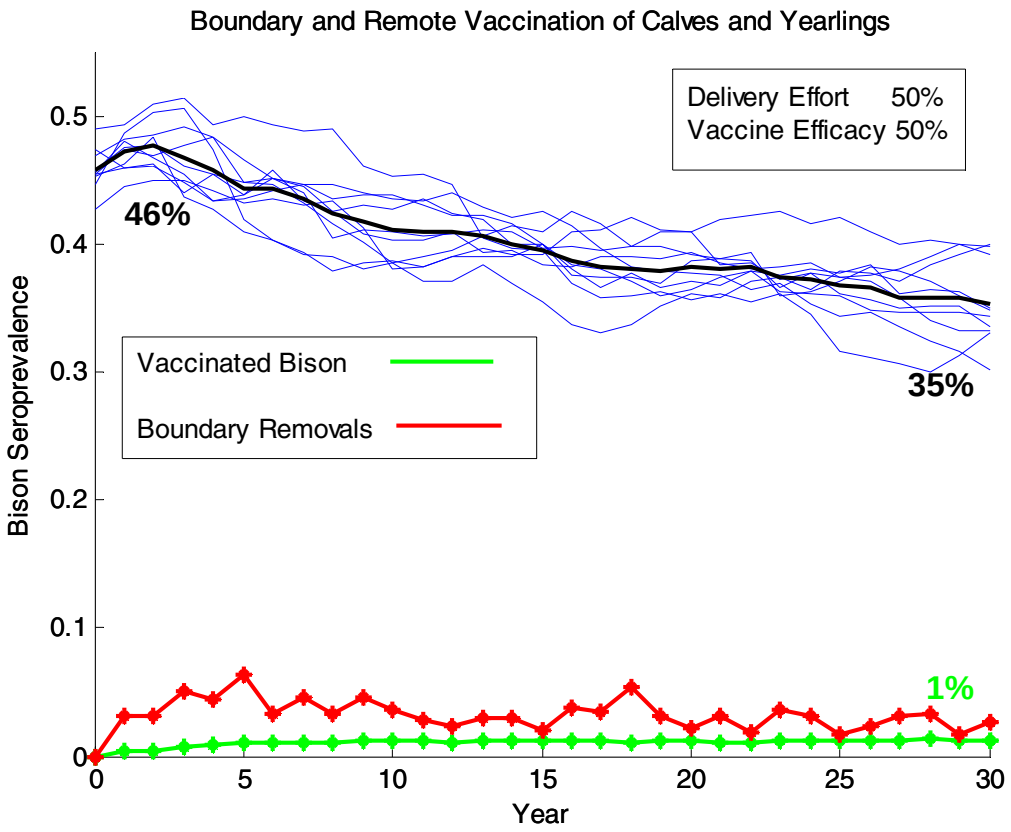


Figure 25. Results of 10 model simulations summarizing seroprevalence declines under alternative A. Captured bison were tested, positive reactors removed, and negative reactors were vaccinated and released. A 24% decline in seroprevalence is estimated over the 30 year period modeled. Under alternative A, more bison are removed at the boundary than vaccinated (1%). The low number of vaccinated bison results in reduction in seroprevalence of 46% to 35% over the 30 year period.

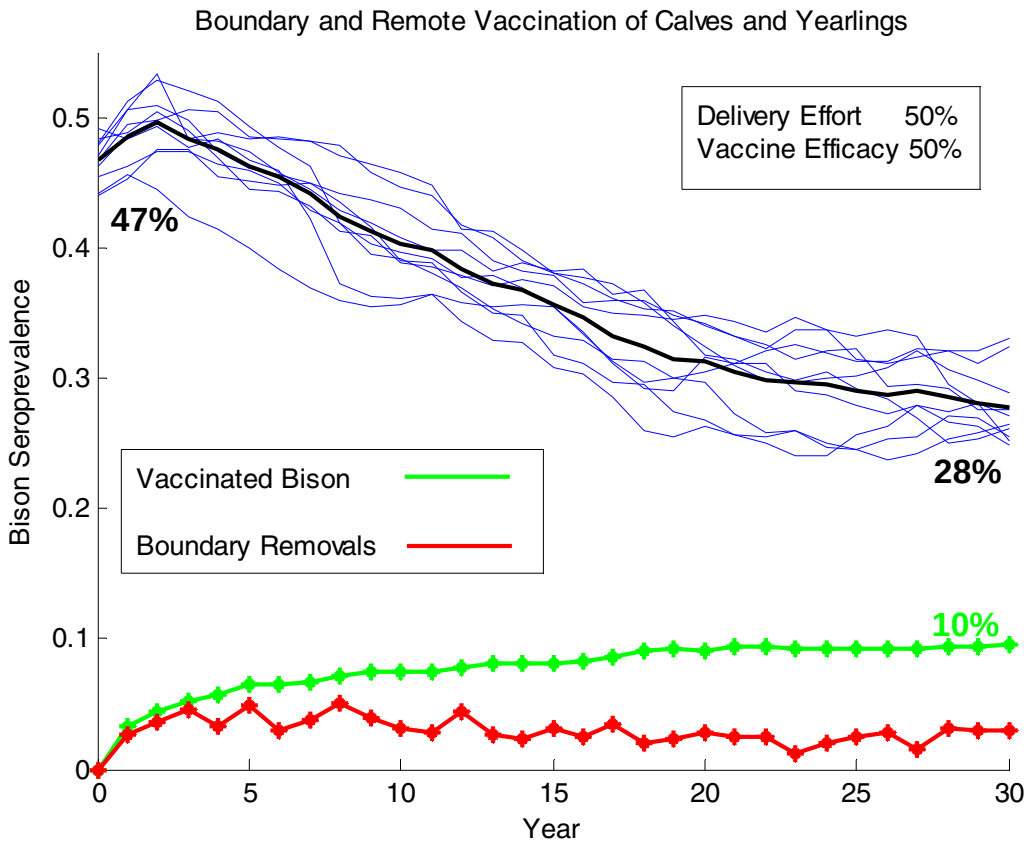


Figure 26. Results of 10 model simulations summarizing seroprevalence declines under alternative B. Bison captured at the boundary were tested, positive reactors removed, and negative reactors were vaccinated and released. Approximately 25% of targeted bison were remotely vaccinated based on intermediate levels of delivery effort and vaccine efficacy. A 40% decline in seroprevalence is estimated over the 30 year period modeled. Under alternative B, more bison are vaccinated (10%) than removed at the boundary. The moderate level of vaccinated bison results in a reduction in seroprevalence from 47% to 28% over the 30 year period.

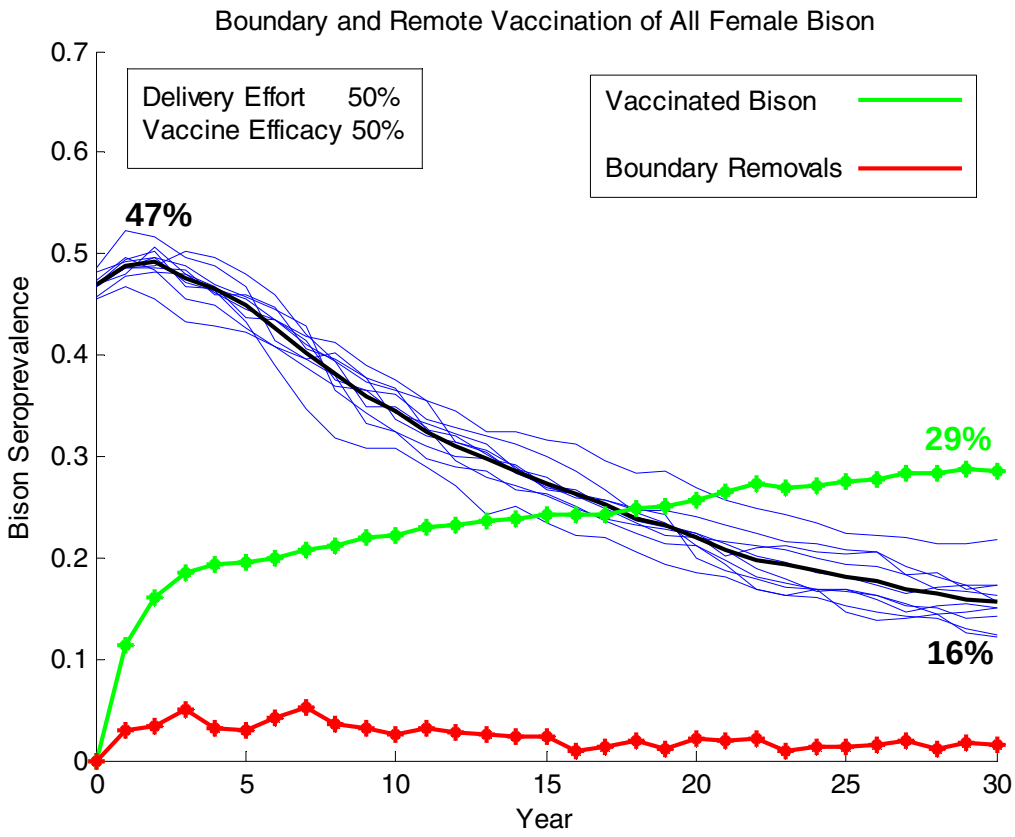


Figure 27. Results of 10 model simulations summarizing seroprevalence declines under alternative C. Bison captured at the boundary were tested, positive reactors removed, and negative reactors were vaccinated and released. Approximately 25% of targeted bison (all females) were remotely vaccinated based on intermediate levels of delivery effort and vaccine efficacy. A 66% decline in seroprevalence is estimated over the 30 year period modeled. Under alternative C, more bison are vaccinated (29%) than removed at the boundary. The high level of vaccinated bison results in a reduction in seroprevalence from 47% to 16% over the 30 year period.

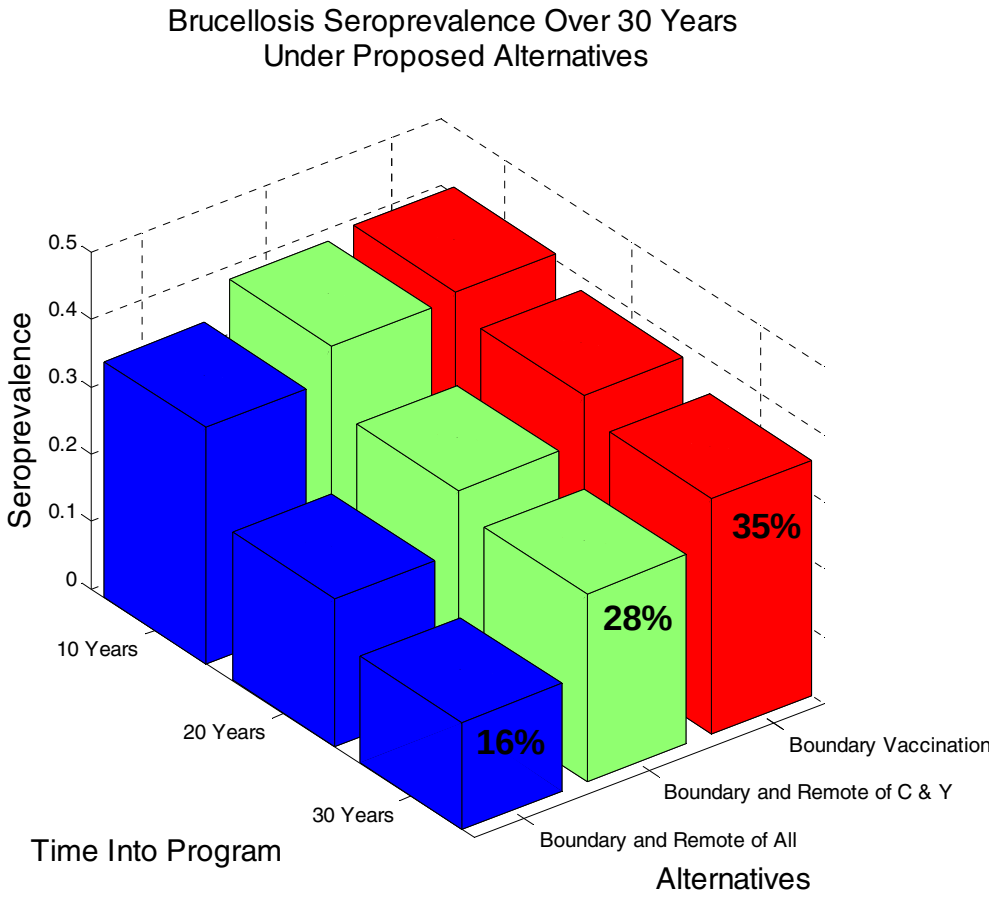


Figure 28. Summary of estimated brucellosis seroprevalence declines in YNP bison under the 3 proposed vaccination alternatives projected over 30 years. Combining boundary management (test, remove, and vaccinate) with remote vaccination of all female bison produces the greatest decline in seroprevalence of the three vaccination alternatives

Appendix I
MODEL DEFINITIONS, RULES, AND ASSUMPTIONS

State Dynamic model

- The model is individual-based and tracks changes in disease state (Infected, Susceptible and Latent disease classes) of all female bison in the population
- Brucellosis transmission is assumed to be dependent on disease state and pregnancy status
- Bull bison are kept track of but not status of individuals (i.e. bulls are put into overall population outputs but are not part of the modeling processes post weaning)

Definitions of disease states:

Susceptible: Bison that have not been exposed *B. abortus.* Susceptible bison are brucella free. All individuals that are in the susceptible class will enter the infected class after exposure to *B. abortus*.

Infected: Bison cows that have been exposed to and ingested *B. abortus* and are actively infectious (developed reproductive tract and mammary gland infections). For this model, an infected cow will abort her next pregnancy at a probability of 0.96.

Latent: This disease state refers to bison cows that have gone through the acute (abortive phase) stage of infection. These bison are harboring live Brucella but are not actively infectious (i.e. cannot shed the disease into the environment or pass it on to a susceptible newborn). Latent cows can relapse (5% of pop change disease state from Latent to Infected during pregnancy) to infectious state and shed *Brucella* at parturition (via infected birth fluids and placenta) and pass infection on to calf (via infected milk that is vertically transmitted to calf with 0.66 probability).

Definition of Vaccinated State:

Vaccinated (V): Bison in this state will be vaccine protected and will not become infected based on the level of vaccine efficacy

i. If a susceptible (S) bison has been vaccinated she enters the 'V' class and is protected from infection at the level of vaccine efficacy (VE) parameter

ii. If cow is infected (I) or latent (L) prior to vaccination she remains in those classes and does not receive protection from the vaccine

Description of Events:

Non-infectious births: During non-infectious birth events, *Brucella* is not shed and these events only result from susceptible and latent (non-relapsing) cows. All calves born in non-infectious births are classified as susceptible.

Infectious births: During infectious births, *Brucella* is shed and these events result from infected and latent (relapsing) cows. Calves born in infectious births can be classified as susceptible (p.34) or infected (p.66).

Recrudescence: Relapses occur in latent bison cows at a specified probability (p.05). These are bison that have gone through the infectious stage of the disease (abortive) and will have an infectious birth if they relapse. Of the 5% that relapse and have infectious births, 66% will pass the disease on to their calf (i.e. vertical transmission occurs in this small number of relapsing bison at a probability of .66)

Exposure: Exposure occurs when a susceptible bison comes in contact with an infectious event (aborted fetus or infectious birth and through vertical transmission). Animals that are exposed during an infectious event change from the susceptible class to the infected class.

Description of select model conditions

Brucella incubation: To induce an abortion or an infectious birth in a newly exposed cow (Susceptible) during gestation, *Brucella* must be incubating at least 35 days. The following outcomes are for the susceptible vaccinated and nonvaccinated disease class at the 2 different incubation times (< 35 days and > 35 days):

Susceptible bison infected with less than 35 days of incubation prior to parturition

- Will not abort or have infectious births
- Calves will be subjected to normal probabilities of vertical transmission.
- Cow will join the latent class.

Susceptible bison Infected with greater than 35 days of incubation prior to parturition

- Cow will abort at probability of .96
- Cow will join the latent class.

Model Assumptions

1. Infectious material in both infectious events (abortions and infectious live births) can be treated equally with regard to disease transmission

2. 46% of seropositive bison are actively infectious based on Roffe et al. (1999)

3. A proportion of latently infected adult cows will recrudesce in any given year and shed *B. abortus* through infectious live births

4. A proportion of calves born via an infectious live birth will be infected through vertical transmission

5. Infected bison never truly recover (clear 100% of bacteria) from brucellosis

6. All actively infected animals and 95% of latently infected bison could be identified using the FPA test during boundary management

7. Assume no additional abortions/mortality with vaccinating adult pregnant bison