This is the author's manuscript for publication. The publisher-formatted version may be available through the publisher's web site or your institution's library.

Modeling the impact of vaccination control strategies on a foot and mouth disease outbreak in the Central United States

Sara W. McReynolds, Michael W. Sanderson, Aaron Reeves, Ashley E. Hill

How to cite this manuscript

If you make reference to this version of the manuscript, use the following information:

McReynolds, S. W., Sanderson, M. W., Reeves, A., & Hill, A. E. (2014). Modeling the impact of vaccination control strategies on a foot and mouth disease outbreak in the Central United States. Retrieved from http://krex.ksu.edu

Published Version Information

1   **Modeling the impact of vaccination control strategies on a foot and mouth disease outbreak in**

2   **the Central United States.**

3

4   Sara W. McReynolds[1], Michael W. Sanderson[1], Aaron Reeves[2], Ashley E. Hill[3].

5

6   [1] Diagnostic Medicine and Pathobiology, College of Veterinary Medicine, Kansas State University,

7   Manhattan, KS 66502

8   [2]Epidemiology Research Unit, Scotland's Rural College (SRUC), Inverness, UK (Reeves);

9   [3]California Animal Health and Food Safety Laboratory, University of California, Davis CA (Hill).

10

11   corresponding author: Mike Sanderson, 785-532-4264, fax 785-532-4851, sandersn@vet.k-

12   state.edu

13

14   **Abstract**

15   The central United States (U.S.) has a large livestock population including cattle, swine, sheep and

16   goats. Simulation models were developed to assess the impact of livestock herd types and vaccination

17   on Foot and Mouth Disease (FMD) outbreaks using the North American Animal Disease Spread

18   Model. In this study, potential FMD virus outbreaks in the central region of the U.S. were simulated to

19   compare different vaccination strategies to a depopulation only scenario. Based on data from the U.S.

20   Department of Agriculture National Agricultural Statistics Service, a simulated population of 151,620

21   livestock operations characterized by latitude and longitude, production type, and herd size was

22   generated. For the simulations, a single 17,000 head feedlot was selected as the initial latently infected

23   herd in an otherwise susceptible population. Direct and indirect contact rates between herds were

24   based on survey data of livestock producers in Kansas and Colorado. Control methods included ring

25   vaccination around infected herds. Feedlots $\geq$3,000 head were either the only production type that was

26   vaccinated or were assigned the highest vaccination priority. Simulated vaccination scenarios included

27   low and high vaccine capacity, vaccination zones of 10 km or 50 km around detected infected premises,

28   and vaccination trigger of 10 or 100 detected infected herds. Probability of transmission following

29   indirect contact, movement controls and contact rate parameters were considered uncertain and so were

30   the subjects of sensitivity analysis. All vaccination scenarios decreased number of herds depopulated

31   but not all decreased outbreak duration.   Increased size of the vaccination zone during an outbreak

32   decreased the length of the outbreak and number of herds destroyed. Increased size of the vaccination

33   zone primarily resulted in vaccinating feedlots $\geq$3000 head across a larger area. Increasing the

34   vaccination capacity had a smaller impact on the outbreak and may not be feasible if vaccine

35   production and delivery is limited. The ability to vaccinate all the production types surrounding an

36   infected herd did not appear as beneficial as priority vaccination of feedlot production types that have

37   high numbers of indirect contacts. Outbreak duration, number of herds depopulated and the

38   effectiveness of vaccination were sensitive to indirect contact transmission probability and movement

39   restrictions. The results of this study will provide information about the impacts of disease control

40   protocols which may be useful in choosing the optimal control methods to meet the goals of rapid

41   effective control and eradication.

42

43   **Introduction**

44

45   Foot and Mouth Disease (FMD) is a highly contagious disease that affects all cloven-hooved

46   animals and is endemic in parts of Asia, Africa and South America. The FMD virus can spread rapidly

47   through susceptible livestock populations prior to the recognition of clinical signs   (Burrows,

48   1968;Burrows et al., 1981); consequently, early detection prior to the spread of the disease is difficult.

49   FMD is a major constraint to international trade because countries currently free of FMD, like the

50   United States (U.S.), take every precaution to prevent the entry of the disease. The U.S. livestock

51   population is naïve to FMD with the last outbreak occurring in 1929 (Graves, 1979).

52   The potential impact of an outbreak in the U.S. would likely be devastating. A secure food

53   supply is vital to the economy with U.S. farms selling $297 billion in agriculture products through

54   market outlets in 2007 (USDA-NASS 2007). In the U.S. the concern for FMD virus re-introduction

55   and the potential economic impacts have risen with the increase of international travel and trade of

56   animals and animal products. At the same time agriculture has become more concentrated with larger

57   capital investments (Hueston, 1993) resulting in increased risk to agricultural production and business

58   continuity.

59   Because FMD is a foreign animal disease in the U.S., there are few avenues available for the

60   study of potential impacts of and effective control strategies for the disease in the event of an

61   introduction. Epidemiological disease modeling is one such avenue. In such models, various control

62   measures, such as movement restrictions, increased biosecurity, depopulation, pre-emptive culling, and

63   vaccination have been implemented in various combinations to evaluate the spread of simulated

64   outbreaks (Ferguson et al., 2001; Gibbens et al., 2001; Bouma et al., 2003; Sutmoller et al., 2003; Perez

65   et al., 2004; Pluimers, 2004; Yoon et al., 2006; Volkova et al., 2011). Depending on the size of the

66   outbreak, timeliness of control implementation, the workforce capacity, and the available resources, the

67   optimal control strategy may vary. The efficacies of different control measures under different

68   conditions can be readily compared using epidemiological modeling.

69   In the U.S., epidemiological disease models have been used to estimate the potential economic

70   impacts of an outbreak. Pendell et al. (2007) estimated economic losses of an outbreak confined to

71   Kansas ranged from $43 to $706 million depending on the type of livestock herd that was initially

72   infected. In an economic model of the impact to the entire U.S., Paarlberg et al. (2002) estimated that

73   a FMD outbreak could decrease U.S. farm income by approximately $14 billion and in 2012 it was

74   estimated that an outbreak originating from the proposed National Bio- and Agri-Defense Facility in

75   Kansas could exceed $100 billion in costs (NBAF, 2012).

76   Epidemiological disease models are dependent on accurate estimates of the frequency and

77   distance distribution of contacts between livestock operations to estimate disease spread and impact,

78   and to guide control measures (Gibbens et al., 2001; Woolhouse and Donaldson, 2001; Dickey et al.,

79   2008; Premashthira et al., 2011). Previous studies that have modeled FMD outbreaks in the central

80   U.S. have relied on expert opinion or contact rates adapted from other regions (Pendell et al., 2007;

81   Greathouse, 2010; Premashthira, 2012). In order to improve the validity of models of this region of the

82   U.S., we used the results of a recent survey of livestock producers (McReynolds et al., 2014a) to inform

83   model parameters used in the current study.

84   The primary objective of this study was to model FMD outbreaks in the Central U.S., using the

85   best available information to establish rates of contact among herds in this region, to identify optimal

86   vaccination control strategies based on their effectiveness in minimizing simulated outbreak durations

87   and numbers of herds depopulated. A secondary objective was to analyze the sensitivity of the model

88   to specific input parameters,including movement controls, direct contact rate, indirect contact rate, and

89   probability of indirect transmission.

90

91   **Materials and Methods**

92

93   *Study Population*

94

95   The number of herds, type of herds and herd sizes at the county level were generated from the

96   U.S. agricultural census 2007 NASS data (NASS, 2007) and adjusted according to criteria by Melius et

97   al. (2006). The study area included Wyoming, South Dakota, Colorado, Nebraska, Kansas, the

98   northern region of New Mexico and Oklahoma, and the Texas Panhandle (Fig. 1). There were 151,620

99   livestock herds in the study area in 2007 (USDA, 2007) including 86,655 cow/calf, 3,232 dairy, 979

100   large feedlots ($\geq$3,000 head), 25,096 small feedlots (<3,000 head), 1,071 large swine ($\geq$1,000 head),

101   6,463 small swine (<1,000 head), 5,159 beef and swine, and 22,965 small ruminant herds (Table 1).

102   NASS data do not account for mixed production types such as beef-swine yet data suggest

103   approximately 7% of Kansas and Colorado herds report having both beef cattle and swine

104   (McReynolds et al., 2014a) To account for this production type seven percent of beef and swine

105   operations were randomly re-designated in the NASS data set from the population of cow/calf

106   operations and small swine in Kansas, Nebraska, Eastern Colorado, and Oklahoma (McReynolds et al.,

107   2014a). The total population was 39,413,228 animals in all production types (Table 1). Heterogeneous

108   random locations within counties were generated for herds using a weighting scheme based on altitude,

109   flatness, and human population developed by Lawrence Livermore National Laboratory for USDA

110   (Hullinger et al., 2009). This method assures that number of herds, number of animals in each herd and

111   production types match at the county level (herds are always allocated to the county they reside in

112   based on NASS data). The geo-located population data set was provided to the authors by USDA.

113

114   *Simulation model*

115

116   The North American Animal Disease Spread Model (NAADSM), an open source) herd-based

117   spatial stochastic epidemic simulation model (Harvey and Reeves, 2010; Harvey et al., 2007) was used

118   to model FMD eradication strategies. Scenarios were simulated for various FMD vaccination

119   protocols, and were compared to a scenario that made use of only depopulation of detected infected

120   herds and traced forward direct contacts of infected herds (Scenario 1). Modeled scenarios are listed in

121   Table 2 and include variations in vaccine capacity, vaccination zone diameter, and the number of

122   infected herds before a vaccination program is initiated. Simulated vaccination protocols included low

123   and high vaccine capacity, which were defined based on results from a Kansas and Colorado livestock

124   producer survey (McReynolds et al., 2014a). The livestock survey asked producers to report the time it

125   would take to vaccinate, tag, and keep records for their entire herd. Vaccination was carried out either

126   for large feedlots only (low vaccine capacity 1 herd per day by day 22 and 3 herds per day by day 40

127   and high vaccine capacity 8 herds per day by day 22 and 15 herds per day by day 40) or for all herd

128   types (low vaccine capacity 5 herds per day by day 22 and 10 herds per day by day 40 and high vaccine

129   capacity 50 herds per day by day 22 and 80 herds per day by day 40). When vaccination capacity was

130   limiting, herds were vaccinated according to a priority scheme based on production type. Vaccination

131   priority from highest to lowest for scenarios where all herd types could be vaccinated was: large feedlot

132   ($\geq$3,000 head), small feedlot (<3,000 head), large swine ($\geq$1,000 head), small swine (<1,000 head),

133   beef-swine, dairy, cow-calf, and small ruminant. Feedlots are prioritized for vaccination because the

134   large number of cattle on a premises makes it difficult to depopulate all of the cattle in a timely fashion

135   and because they are terminal animals that fit a vaccinate to slaughter strategy thus conserving

136   destruction capacity and production value. The low vaccine capacity was to simulate administration by

137   USDA personnel and the high capacity producer administration of vaccine. The vaccinated animals

138   remain in the population unless infected after their immune period ends.

139   The distributions for within herd prevalence of FMDV for NAADSM were produced using a

140   within herd prevalence model (WH) (Reeves, 2012a) based on estimates for the latent, subclinical

141   infectious, and clinical infectious stages. The WH model operates at the level of the individual animal,

142   and incorporates sources of individual-level variation such as variability in the durations of incubating

143   and infectious periods, the stochastic nature of the disease spread among individuals, the effects of

144   vaccination, and disease mortality (Reeves, 2012b). Distributions of the clinical stages of FMD in

145   individual animals were based on a meta-analysis of the duration of the disease states where the

146   infectious period was reported including the subclinical and clinical periods (Mardones et al., 2010).

147   The reported clinical period in Mardones et al., (2010) is the time when clinical signs are apparent

148   which includes a period when the animal is no longer infectious. The WH model requires durations for

149   the latent, subclinical infectious and clinical infectious stages. Distributions for the latent and

150   subclinical states were used directly as they are reported in Mardones et al. (2010) but the reported

151   distributions were not suitable for the clinical infectious period in WH and required adjustment for the

152   period when the animal is not infectious. As reported in figure 1of Mardones et al. (2010) the

153   Subclinical period + Clinical period = Infectious period

154   *therefore*

155   Infectious period - Subclinical period = Clinical period

156   The clinical infectious period distribution for cattle, swine and small ruminants was calculated for *WH*

157   by using monte-carlo simulation (@Risk 5.01, Palisade Corp., Ithaca, NY, USA) to sample 10,000

158   values from the subclinical infectious period and the infectious period reported in Mardones et al.

159   (2010). When the sampled value from the infectious period was greater than the sampled value for the

160   subclinical period, the value for the subclinical period was subtracted from the sampled values for the

161   infectious period. The resulting distribution of values was fit to a theoretical distribution (@Risk 5.0.1)

162   to estimate the clinical infectious period for use in WH to estimate the within herd prevalence over time

163   for each production type. The probability of infection following a direct contact in NAADSM was

164   based on within-herd prevalence of the infected herd as a function of time since infection.

165   Model parameters were set to allow virus to spread by direct contact, indirect contact, and

166   airborne/local spread. In NAADSM a direct contact represents the movement of infected livestock

167   between premises. An indirect contact represents the movement of a fomite such as contaminated

168   vehicle, equipment, clothing, or a person between premises. Direct and indirect contacts between

169   livestock production types were based on a livestock contact survey in the central U.S. (McReynolds et

170   al., 2014a) (Appendix Tables A1 and A2). The direct contact rate was calculated from the reported

171   count of contacts between specific production types to provide an overall production type specific

172   number of contacts per day. Destination to source combinations for indirect contact were calculated

173   based on the total number of indirect contacts reported for each production type, multiplied by the

174   proportion of all indirect contact made to the respective production type to produce the number of daily

175   indirect contacts between each destination to source combination. For example if cow-calf operations

176   received 0.7 total visits from potential indirect contacts per day, and 18.8% of all potential indirect contacts

177   (across all production types) were to Cow-Calf operations then in 0.133 visits per day the previous production

178   type exposure of the indirect contact was a Cow-Calf operation resulting in an indirect contact between two

179   Cow-Calf operations (0.7*18.8% = 0.133 contacts per day as shown in Table 2A). The daily indirect contact

180   rate between each production type was adjusted based on the assumption that not all production types

181   are equally connected (e.g. beef operations are more connected with each other than with swine

182   operations). The daily mean number of direct and indirect contacts between production types were

183   used to parameterize the model. Generation of actual direct and indirect contacts between production

184   types in the NAADSM model were stochastically generated for each infected herd each day from a

185   Poisson distribution with lambda equal to the calculated mean contact rate (direct and indirect) for that

186   production type combination (Tables A1 and A2). Specific susceptible recipient herds of direct or

187   indirect contacts were selected based on a random draw from the respective distance distribution for

188   contacts between specific production types (Tables A1 and A3). The probability of airborne/local

189 spread at 1 km was 0.5% per day and declined linearly to 0% at the maximum distance of spread of 3

190 km. The probability of local/airborne transmission was calculated based on distance between the

191 infected and susceptible herd, herd size and within herd prevalence. Actual transmission between the

192 infectious and susceptible herd was generated based on generation of a random number r between 0

193 and 1 where infection is transmitted when r is less than the calculated probability of transmission.

194   Days to first disease detection was a generated output by the NAADSM model based on the

195 probability of disease recognition within infected herds as a function of the amount of time the herd has

196 been clinical infectious. Actual detection of a clinical herd (both the initial and subsequent herds) was

197 based on generation of a random number r between 0 and 1 where the infected herd is detected when

198 when r is less than the calculated probability of recognition. The probability of recognition increased

199 over time within a herd peaking at 100% by day 10 in all herd types except small ruminants where

200 recognition probability did not reach 100% until day 14 following introduction of disease to that herd.

201 For all scenarios,

202   a) All herds detected positive and the forward traced direct contacts of detected herds were

203   depopulated.

204   b) The probability of indirect disease transmission following indirect contact between an

205   infected and susceptible herd was held fixed at 20% for all production types except swine

206   which was set at 30% to account for increased FMD virus shedding by swine based on

207   subject matter expert opinion solicited by USDA.

208   c) Direct contact through animal movement was linearly reduced to 10% of pre-outbreak

209   levels and indirect contacts were linearly reduced to 30% of pre-outbreak levels by day 7

210   after the first disease detection to allow for time delays in implementation and enforcement

211   of movement controls based on subject matter expert opinion solicited by USDA.

212   d) Depopulation capacity was linearly increased from 0 to 8 herds/day by day 10 and 16

213   herds/day by day 30 after first disease detection.

214　　　　　e)　A 100% effective quarantine of infected premises and a ban on livestock movement from

215　　　　　　　known infected premises was assumed.

216　Depopulation was set to begin on day 2 after first disease detection of the outbreak.　All scenarios

217　were run for 200 iterations.　The mean, 5th and 95th percentiles of outbreak duration, number of

218　destroyed herds and number of animals vaccinated were monitored for convergence. The end of the

219　active disease phase (i.e., the point in time at which no infected herds remained in the population) was

220　the endpoint for all scenarios.　Conditions of the NAADSM model used in this study of a hypothetical

221　outbreak in the central U.S.were:

222　　　　　a)　There are eight defined livestock operation production types in the study region (Table 1)

223　　　　　　　and wildlife are not included.

224　　　　　b)　All herds in the same production type have the same disease parameters.　Probability density

225　　　　　　　functions characterize the length of the disease periods and this length is determined

226　　　　　　　stochastically by a random draw from the distributions for each new infected herd.

227　　　　　c)　The population is closed and constant.　Herds only exit the population by depopulation.

228　　　　　d)　There is no mortality from FMD during the simulated outbreak.

229　　　　　e)　There are no virus carrier states for recovered animals.

230　　　　　f)　Vaccine is 100% effective following a 7 day delay after vaccination.

231　　　　　g)　Quarantine of infected herds is 100% effective for all contacts and implemented until the

232　　　　　　　herd is depopulated.

233　　　　　h)　Detection of positive herds was based on the probability of visual, clinical disease

234　　　　　　　recognition within infected herds as a function of time the herd has been clinical infectious.

235

236　*Experimental design*

237

238　　　　　In all scenarios, a single 17,000 head feedlot in Northeast Colorado was latently infected and

239   served as the index herd for the outbreak. Seventeen different disease mitigation scenarios were

240   simulated as described in Table 2.

241

242   *Sensitivity Analysis*

243

244   Values of selected uncertain parameters were varied from baseline values in a sensitivity

245   analysis to assess their independent influence on the disease modeling results. The 17 scenarios were

246   simulated for each variable change. The baseline probability of transmission given indirect contact was

247   20% and the sensitivity analysis assessed it at 15% and 25%. Sensitivity analysis of the contact rates

248   were also completed with the direct contact rates adjusted to +/- 20% and +/-50% of the baseline rate

249   parameter. Sensitivity of the indirect contact rates for each production type combination was assessed

250   by changing all production type combination rates by +/- 20% from the calculated parameter for all

251   scenarios. Lastly the influence of indirect movement controls was assessed by changing the baseline

252   indirect movement control of 30% of pre-outbreak levels to 20% and 40% of pre-outbreak movement

253   levels to represent a relatively wide range of indirect movement control.

254

255   *Data analysis*

256

257   The NAADSM model produced results for each day of the outbreak for each iteration. The

258   results from each scenario were aggregated into weekly outcome counts for each iteration of each

259   scenario. Summary statistics were generated for each of the scenarios. Outbreak duration was

260   calculated from the first day of the simulation to the end of the active disease phase of the outbreak.

261   Analysis was performed in commercially available software (Stata12.1, (StataCorp., 2011) and in open

262   source 64 bit *R* 2.15.2 (R development core team, 2011). To test the statistical differences between

263   scenarios, a Kruskal-Wallis one-way analysis of variance was used to identify significant differences in

264   outbreak duration and number of herds depopulated controlling for multiple comparisons at $p<0.05$

265   according to the method of Holm (1979) implemented in *R*.

266

267   **Results**

268

269   The mean, 5th and 95th percentiles of outbreak duration, number of destroyed herds and

270   number of animals showed less than 4% change at 200 iterations for all scenarios. Most scenarios

271   converged at approximately 100 iterations and all scenarios converged before 200 iterations. In all

272   scenarios the main source of new infections was indirect contacts; approximately 95% of infected herds

273   resulted from an indirect contact and the remaining 5% were infected from direct contact or

274   airborne/local-area spread. In all scenarios the median first day of detection was at 10 or 11 days. The

275   median day of first vaccination was 17-22 days following first detection for scenarios where

276   vaccination was initiated after 10 herds were detected positive. For scenarios where vaccination was

277   initiated after 100 herds were detected the median day of first vaccination was 57-65 days after the first

278   detection.

279   For scenario 1 with no vaccination, there was a sharp peak in the weekly number of detected herds

280   compared to the scenarios with vaccination (Figure 2). In scenario 1 there were 104 new herds

281   detected during week 18 and during week 28, 342 herds were detected. By comparison, in scenario 2,

282   which used a small vaccine capacity and small vaccination zone, 74 new herds were detected during

283   week 18 and 60 herds were newly detected during week 28. The total median number of herds

284   detected as clinically infected per outbreak in scenario 1 was 10,139, which represented approximately

285   6.5% of the herds in the region. All vaccination scenarios had fewer detected clinical herds: for

286   example, scenario 2 had a median of 2,183 clinically infected herds per outbreak, and scenario 4 had a

287   median of 419 clinically infected herds per outbreak.

288

289   *Outbreak Duration*

290   The model outcomes are reported in Table 3. The scenarios with vaccination zones of 50 km

291   (scenarios 4, 5, 8, 9, 12, 13, 16, and 17), had a shorter median and 90th percentile durations compared to

292   the scenarios with 10 km vaccination zones (scenarios 2, 3, 6, 7, 10, 11, 14, and 15): the best eight

293   ranked scenarios for shortest median duration all had 50 km vaccination zones (Table 3). Scenario 16

294   had the shortest median outbreak duration, followed by scenarios 4, 8, 12, and 17. The vaccination

295   capacity and the number of herds infected prior to starting vaccination had less impact on median

296   outbreak duration than the size of the vaccination zones: scenarios with both high and low vaccination

297   capacity and number of herds infected to initiate vaccination were among the top ranked scenarios.

298   Scenario 1 ranked 10th in median outbreak duration. Scenarios 7, 10, and 2 had the three longest

299   median outbreak durations and all had vaccination zones of 10 km. Additionally, scenarios 7 and 10

300   had a late vaccination trigger of 100 herds infected prior to the initiation of vaccination.

301

302

303   *Depopulation*

304   All vaccination scenarios decreased the median number of herds depopulated compared to

305   scenario 1. The 7 scenarios with the lowest median number of depopulated herds all had a vaccination

306   zone radius of 50 km, ranging from median numbers of depopulated herds from 252 to 1,735. Scenario

307   1 had a median of 6,890 herds depopulated per simulated outbreak. The distribution was heavily

308   skewed toward larger numbers depopulated (Table 3). In scenario 1, the median number of herds

309   depopulated included all large feedlot and dairy herds in the population. Also, scenario 1 was the only

310   scenario with herds waiting to be depopulated at the end of the active disease phase (median 2,830

311   herds waiting per simulated outbreak, data not shown). Scenario 16 depopulated the fewest number of

312   herds followed by scenarios 4, 8, and 17 which did not significantly differ from one another.

313

314   *Vaccination*

315   In the best 8 scenarios in terms of vaccinating the smallest median number of herds, only large

316   feedlots were vaccinated. None of these scenarios were among the best scenarios in terms of median

317   outbreak duration or median number of herds depopulated. Scenario 11 vaccinated the fewest number

318   of herds followed by scenarios 3 and 7, which did not differ significantly from each other (Table 3).

319   The only scenarios in which all production types were vaccinated were scenarios 6 and 14, which had a

320   high vaccine capacity and a small zone size. Due to vaccine capacity in the remaining scenarios, only

321   large and small feedlots were vaccinated. The number of herds vaccinated differed greatly between the

322   scenarios. Scenarios 16 and 8 had a high vaccine capacity with large feedlots having first priority and

323   vaccinated approximately 10,000 herds, compared to scenarios 4 and 12, which had a low vaccine

324   capacity and vaccinated approximately 1,800 herds. However, in scenario 17 only large feedlots were

325   vaccinated resulting in 1,329 herds vaccinated and the number of herds depopulated was similar to

326   scenarios 4, 8 and 12.

327   In scenarios with large feedlot vaccination priority, a large vaccination zone and high vaccine

328   capacity (scenarios 8 and 16) there was a sharp peak at the beginning of the outbreak in the number of

329   animals vaccinated but it dropped off sooner than the scenarios with a small zone and high capacity

330   (scenarios 6 and 14) (Figure 3). The median of the maximum number of animals vaccinated in a 1

331   week period ranged from 163,124 to 963,427, and the maximum 90th percentile ranged from 251,883 to

332   2.5 million animals in one week depending on vaccine capacity and zone size.

333

334   *Sensitivity analysis*

335   When the probability of transmission following indirect contact was increased to 25% and

336   decreased to 15%, it was influential in determining the duration of the outbreak, the number of herds

337   depopulated, and the numbers of herds and animals vaccinated.   Vaccination was less beneficial in

338   mitigating the effects of an outbreak when probability of transmission following indirect contact was

339   decreased to 15%. In all such scenarios, the median duration of the outbreak was approximately 100

340   days (range 93-150) (Figure 4) and the median number of herds depopulated was approximately 50

341   (range 36-83) (Figure 5). The number of herds depopulated decreased by over 90% in most scenarios

342   (range 82-99%) when the probability of indirect transmission was 15%, and increased by over 200% in

343   all but scenario 1 when the probability of indirect transmission was 25% (range 218-1381%). When

344   the probability of indirect transmission was 25% the median duration of the outbreak was over 500

345   days for most scenarios (range 418-792) (Figure 4), and the median number of herds depopulated was

346   over 5000 for all scenarios except 8, 16 and 17 (Figure 5). In scenarios with vaccination zones of 50

347   km, when the probability of indirect transmission was increased to 25%, the median duration of the

348   outbreak increased by over 100% compared to an increase of less than 5% in the scenarios with

349   vaccination zones of 10 km. All scenarios with a vaccination zone of 50 km except scenario 12 still

350   had shorter duration and fewer herds depopulated compared to scenarios with a 10 km vaccination

351   zone.

352   Changes in the effectiveness of indirect contact movement controls were also influential within

353   the range examined in determining the outbreak duration, the number of herds depopulated and

354   vaccinated (Figures 7, 8, 9). When indirect movement controls were increased to achieve 20% of pre-

355   outbreak levels (as opposed to 30% in the baseline scenarios), the median duration of all scenarios was

356   approximately 100 days (range 85-120) (Figure 7). The median numbers of herds depopulated

357   decreased 65-95% to approximately 50 herds (range 39-66) in all scenarios (Figure 8). When indirect

358   movement controls were set at 40% of pre-outbreak levels, median duration of the outbreak was

359   approximately 500 days for all scenarios (range 481-726) (Figure 7), and the median number of herds

360   depopulated increased over 200% for all but scenario 1 to over 5000 for all scenarios except 8 and 16

361   (Figure 8).

362   Changes in the indirect contact rates between herds were influential in the number of herds

363   depopulated, but less so on outbreak duration. When indirect contact rates were decreased by 20% the

364   10th percentile of outbreak duration was decreased approximately 25-72% and the median by 33-72%

365   (Figure 10). Median number of herds depopulated decreased 65-97% to 58 to 584 herds (Figure 11).

366   When indirect contact rates were increased by 20% the median number of herds depopulated increased

367   60-89% to greater than 5,000 herds for all scenarios except 4, 8, 16 and 17.

368   Sensitivity analysis scenarios ranked similarly to the baseline with scenario 16 or 17 always

369   having the fewest median number of herds depopulated for all sensitivity scenarios.   Scenarios 8 and 4

370   were also among the best ranking scenarios for the lowest median number of herds depopulated.

371   Scenario 1 was ranked in the best 5 scenarios for number of herds depopulated when movement

372   controls were either 20% or 40% of pre-outbreak indirect contact levels or when the indirect contact

373   rate was increased by 20% (Table 4). The sensitivity analysis scenario rankings for outbreak duration

374   showed more variation from the baseline and among the sensitivity scenarios. Scenario 4 was always

375   among the best five scenarios for outbreak duration and scenario 16 was among the best five in all

376   sensitivity scenarios except when indirect movement control was 40% of pre-outbreak indirect contact

377   levels. Scenario 1 was ranked best for outbreak duration when indirect movement control was 40% of

378   pre-outbreak indirect contact levels and among the best five scenarios for outbreak duration when

379   indirect transmission probability was 25% and when the indirect contact rate was increased by 20%

380   (Table 4).

381   Increasing direct contact rate by 20% or 50% had little impact of the outcome of the results

382   (data not shown).

383

384   **Discussion**

385   *General discussion*

386   Modeling is a widely used method for assessing the impact of an FMDV introduction in the

387   U.S. and the effectiveness of control because of its nature as a highly infective foreign animal disease.

388   Control methods in the face of an outbreak of FMD include movement controls on livestock and

389   support industries, increased biosecurity such as disinfection of traffic on and off the farm, slaughter of

390   affected and in contact or high risk animals, and vaccination. In this study probability of indirect

391   transmission, movement controls, and vaccination protocols were analyzed to determine the impact of

392   the different control methods. We interpret probability of indirect transmission as a surrogate for

393   disinfectant or biosecurity practices on farm in the sensitivity analysis.

394   The number of herds depopulated was greatest for scenario 1 and the least for scenario 16

395   (Table 3). In scenario 1, the number of herds depopulated was much higher than the scenarios that

396   included vaccination. The outbreak in scenario 1 spread rapidly and it was the only scenario with herds

397   waiting to be depopulated at the end of the active disease phase, having exceeded the depopulation

398   capacity. Scenario 16, which had a large vaccination capacity as well as a large vaccination zone, was

399   able to contain the spread. Due to workforce and vaccine capacity, the high capacity vaccination in a

400   large zone might not be feasible during an outbreak. In the scenarios with a larger vaccination zone,

401   vaccination was advantageous in controlling depopulation and duration suggesting a threshold level of

402   vaccination necessary to bring the outbreak under rapid control. The results reported here represent

403   onset of immunity at 7 days after vaccination and a predominantly indirect contact infection challenge.

404   These results support the value of vaccination strategies, particularly those with large vaccination

405   zones, to control disease impact. The model assumed 100% vaccine efficacy so this is clearly an upper

406   bound of the potential vaccine effect. NAADSM does not currently allow for variation in vaccine

407   efficacy and further studies examining the effect of vaccine are warranted. High potency vaccines

408   formulated for emergency vaccination have shown 100% efficacy by 2-4 days after vaccination in

409   small studies of cattle and pigs challenged by indirect aerosols (Cox and Burnett, 2009). Efficacy was

410   only 70-75% at 10 days after vaccination when a direct exposure to shedding animals was used as the

411   challenge (Cox and Burnett, 2009).

412   Scenarios 7, 10, and 2 (each of which had small vaccination zone and low vaccination capacity)

413   had a longer duration of outbreak when compared to scenario 1 (only depopulation). The duration of

414   the outbreak may potentially be shorter in scenario 1 due to rapid expansion and burnout without

415   vaccination to slow the spread of the virus. Limited vaccination programs may reduce the number of

416   infections without effectively bringing the outbreak to an end. Perez et al. (2004) concluded from the

417   Argentina outbreak in 2001 that mass vaccination can be useful in controlling a large epidemic but that

418   it could take a long time to bring the outbreak under control (Perez et al., 2004). The number of herds

419   depopulated in the results reported here however, was decreased in all vaccination scenarios including

420   scenarios 2, 7 and 10. Based on number of herds depopulated, scenario 2, 7, and 10 control methods

421   are advantageous compared to scenario 1 despite the longer duration of outbreak. An economic

422   analysis of a subset of these scenarios however indicated that outbreak duration was a major

423   determinant in increasing outbreak cost (Schroeder et al. accepted).

424   Despite the large region represented in the model, in reality not all movements would be

425   confined to the modeled area as in this hypothetical FMD outbreak, so a real outbreak could spread

426   further. The duration of a hypothetical epidemic modeled in the Texas Panhandle region had a median

427   of 25-52 days (Ward et al., 2009) which was much shorter than the results in the study reported here

428   where median duration ranged from 181-608 days. Ward et al. (2009) was confined to an eight county

429   region and the outbreak could easily be larger following spread to other regions. We chose an initially

430   latent herd in the central location of our population to allow the most geographic freedom of disease

431   spread and minimize any geographic boundary effect in the results.

432   The median number of herds detected as clinically infected for scenario 1 represented

433   approximately 6.5% (10,139 /151,620) of the herds in the study population and scenario 2 represented

434   1.4% (2,183/151,620) of the herds. The results of scenario 2 are comparable to the 2001 U.K. FMD

435   outbreak where 1.4% of herds (2030/146,000) were reported as infected (Anderson, 2002) and an FMD

436   model of 3 counties in California where 2% of herds were infected (Bates et al., 2003b). In the study

437   reported here, scenario 16 had the lowest number of infected herds detected at 0.16% followed by

438   scenario 4 at 0.3% of the herds detected as clinically infected.

439   Our data is consistent with a large vaccination zone having the biggest impact on the duration of

440   the outbreak. Bates et al. (2003b) found that vaccinating all herds within 50 km of an infected herd

441   was an effective strategy to reduce duration of the outbreak when modeling an FMD outbreak in a 3-

442   county region of California. In that regional study the outbreaks in scenarios with the large vaccination

443   zone lasted the shortest number of days despite not all the herds in the zone getting vaccinated due to

444   capacity limitations.

445   Our low vaccination capacity scenarios were meant to represent vaccine administration by

446   USDA personnel only. Livestock production type had priority over days waiting in queue for

447   vaccination so the only scenarios where any production type besides feedlots were vaccinated were

448   scenarios that had a high vaccination capacity and a small vaccination zone. However, these small

449   zone and high capacity scenarios had outbreaks that lasted longer, leading to more herds being

450   vaccinated compared to high capacity and large zone scenarios. The two scenarios that had the highest

451   number of herds vaccinated (scenarios 14 and 6) had high vaccination capacity, a small zone,

452   vaccinated all herd types and exceeded 30,000 herds vaccinated. However, they were never among the

453   top ranked scenarios for outbreak duration or number of herds depopulated. Because of the high

454   percent of infections resulting from indirect contacts in these models, the ability to vaccinate all the

455   production types surrounding an infected herd did not appear as beneficial as priority vaccination of

456   feedlot production type that have high numbers of indirect contacts.

457   The high vaccine capacity scenarios were meant to represent vaccination being carried out by

458   the farmers and ranchers as was done in the 2001 Uruguay outbreak. Data from the Uruguay outbreak

459   indicates an average vaccination rate of 350,000 cattle per day in each round of vaccination (Sutmoller

460   et al., 2003) which is a higher rate than the requirement in our high vaccine capacity scenarios where

461   the median of the maximum animals vaccinated in a 1 week period was 963,427, and similar to the 90th

462   percentile (2.5 million animals in one week). In the U.S., animal health officials could have some

463   concerns regarding producers administering FMD vaccine themselves, as it is a restricted and

464   controlled vaccine. While reliable procedures for administering vaccine and identifying vaccinates

465   would be necessary, allowing producers and private veterinarians to perform vaccination would

466   increase the capacity dramatically.

467   Minimizing the number of herds vaccinated is not the most appropriate measure of the best

468   vaccination strategy, but is useful for identifying the most efficient use of vaccination. The scenarios

469   with the shortest duration of outbreak and the lowest number of herds depopulated varied in the number

470   of herds vaccinated, but were consistently scenarios with large vaccination zones.

471   The top five ranking scenarios for outbreak duration and number of depopulated herds

472   contained scenarios with both 10 and 100 herds infected prior to the initiation of vaccination suggesting

473   the decision to vaccinate may not need to be made at the very beginning of the outbreak allowing

474   additional time to produce adequate vaccine supplies to meet demand and to evaluate the need for

475   vaccination. These results also suggest that a proper vaccination plan could decrease the number of

476   personnel needed for depopulation to partly make up the likely increased personnel requirements to

477   implement vaccination. Vaccination zone size was the most important factor determining the outbreak

478   duration and the number of herds depopulated. All five top ranked scenarios for the duration of the

479   outbreak and number of herds depopulated had large vaccination zones. Vaccination does not require

480   the time or the quantity of labor that are needed for depopulation and disposal of carcasses. The

481   disadvantages of vaccination are imperfect efficacy, the delay before protection of almost a week (Salt

482   et al., 1998), the challenge of producing sufficient quantities of strain specific vaccine, the lack of cross

483   immunity between strains, and the trade implications of vaccinating and recovering disease free status

484   (Office International des Epizooties/World Organisation for Animal Health, 2013).

485   Some previous research has found that vaccination protocols in the control of a FMD outbreak were not

486   economically beneficial (Schoenbaum and Disney, 2003; Elbakidze et al., 2009). Bates et al. (2003) in

487   a benefit-cost analysis model of a FMD outbreak in 3 counties in California, found vaccination would

488   be a cost-effective strategy if vaccinated animals were not subsequently depopulated (Bates et al.,

489 2003a). Vaccinated herds in the scenarios reported here were not depopulated and all vaccination

490 scenarios in this study did decrease the number of herds depopulated compared to depopulation only.

491 Further, an economic analysis of these results found that vaccination was also advantageous to

492 decreasing the median economic impact of the outbreak (Schroeder et al., accepted).

493   FMD simulation models have found that targeting high-risk production types can increase the

494 efficiency of vaccination (Keeling et al., 2003). In the current study large feedlots were prioritized for

495 vaccination due to their high contact rate and the large number of feedlots in the central region of the

496 U.S.   Large feedlots have a high number of indirect contacts (McReynolds et al., 2014a) potentially

497 increasing their risk of becoming infected and spreading infection during an outbreak. In this study, the

498 scenarios with large vaccine zones and feedlot vaccination priority, predominantly vaccinated large and

499 small feedlots but had a similar impact on the outbreak as scenarios where only large feedlots were

500 vaccinated. Scenario 17 is of note as a top ranking large feedlot only vaccination scenario with high

501 capacity (8 herds by 22 days and 15 herds by 40 days) and large vaccination zone. This suggests there

502 may be methods to efficiently apply vaccination to high risk groups and efficiently use resources

503 (Keeling et al., 2003; Keeling and Shattock, 2012). Animals in large feedlots are also a natural

504 vaccinate to die (slaughter) population perhaps facilitating restoration of FMD free without vaccination

505 status, without the cost of depopulation or the loss of valuable protein for human nutrition. However,

506 vaccinating to live versus to die has different implications from an international trade perspective. In

507 vaccinate to live scenarios, export market access would likely be delayed at least 3 additional months

508 relative to a depopulating all vaccinated animals.

509

510 *Sensitivity of input values*

511   The operational validity of the model was assessed using a sensitivity analysis to determine the

512 impact of uncertainty in contact and control methodologies (Frey and Patil, 2002; Garner and

513 Hamilton, 2011). Indirect contacts are a potential risk for disease spread particularly for a highly

514   contagious disease such as FMD (Cottral, 1969; Ellis-Iversen et al., 2011) and in our scenarios

515   approximately 95% of the infections were transmitted through indirect contacts. The sensitivity

516   analysis was used to determine the impact of changes in the disease control methods and the contact

517   rates on the model results. The sensitivity analysis of the direct contact rate demonstrated that the

518   model was not sensitive to changes in the direct contact rate, which may be due in part to the 100%

519   quarantine of infected herds within the model. The model was sensitive to changes in the indirect

520   contact rate. This highlights the need for accurate data regarding indirect contacts between livestock

521   producers. Indirect contact rates used here are based on a survey of producers in Kansas and Colorado

522   (McReynolds et al., 2014a) representing all modeled production types and provide the best available

523   estimates of direct and indirect contacts between production types for the region being simulated.

524   When the indirect contact rates for all production types were decreased by 20%, the median duration of

525   the outbreak and number of herds depopulated decreased substantially. The ranking of the best

526   scenarios by number of herds depopulated remained similar (Table 8) but the impact of vaccination was

527   substantially decreased.

528   When the indirect contact rates increased 20%, scenarios with a small vaccination zone had

529   larger outbreaks than scenario 1. Again scenario 1 did appear to spread quickly with the number of

530   herds exposed to the virus and waiting for depopulation being the largest of all the scenarios. When the

531   indirect contact rate was increased the number of infected herds increased rapidly and the vaccination

532   capacities modeled were not sufficient to control the outbreak. In the face of an outbreak that is

533   spreading rapidly vaccine capacity appears to be important. In the Taiwan outbreak inadequate vaccine

534   supply was one of the potential factors in the large epidemic (Yang et al., 1999). This may also be a

535   factor in our scenarios where the vaccination zone was small and the outbreak lasted longer than the

536   depopulation alone scenario.

537   Due to the impact of movement controls on an agriculture community and on animal welfare, a

538   sensitivity analysis on the impact of movement controls within the model was simulated. Feed

539   delivery, supplies, and labor are indirect movements that must be maintained for business continuity

540   and for animal welfare reasons in the face of a FMD outbreak. The minimum amount of movements

541   that will be necessary will vary for different production types. Decreasing indirect movement from

542   30% to 20% of pre-outbreak levels substantially decreased the number of herds depopulated and the

543   duration of the outbreaks to similar levels in all scenarios. None of the vaccination scenarios were

544   different from scenario 1 for number of herds depopulated and duration of outbreak. While decreasing

545   movement was effective in decreasing the number of herds depopulated, the ability to achieve a

546   decrease in indirect movement to 20% of the pre-outbreak level without animal welfare issues is not

547   clear. The animal welfare consequence of these movement controls on un-infected or infected herds

548   awaiting depopulation has been found to be significant (Laurence, 2002). If this level of movement

549   control is achievable in the face of an outbreak consistent with acceptable animal welfare, it may be

550   sufficient and vaccination may have little additional benefit. When indirect movement control was set

551   at 40% of pre-outbreak levels, the duration of the outbreaks were all similar to scenario 1, lasting 500

552   to 700 days and scenario 1 had the third lowest number of herds depopulated. This demonstrates that if

553   strict indirect movement controls are not possible, vaccination might not be effective in disease

554   outbreak control. Because the range of estimates of indirect movement control (20% to 40% of pre-

555   outbreak levels) used in the sensitivity analysis identified substantial variation in the outcomes,

556   additional estimates outside that range were not evaluated. Achievable movement controls consistent

557   with acceptable animal welfare require additional investigation to support more refined modeling.

558   Probability of transmission given an indirect contact showed a similar effect in the sensitivity

559   analysis. When the probability of indirect transmission was decreased from 20% to 15% the number of

560   herds depopulated and the outbreak duration decreased substantially in all scenarios. The probability

561   of transmission following indirect contact between an infected and susceptible herd could represent a

562   measure of the biosecurity practices applied to traffic and people on and off the farm. Important

563   aspects include truck washing, boot washing and control of visitor contact with animals. With

564   increased biosecurity, vaccination did not offer any benefit over the depopulation alone control strategy

565   but again the impact and ability to achieve this level of biosecurity is unknown. Increased biosecurity

566   would be an important aspect of control efforts and could be a welfare friendly option to control spread

567   compared to increased movement controls. Alternately, decreased probability of transmission

568   following indirect contact may be representative of FMD strains with lower transmissibility. When the

569   probability of transmission given an indirect contact was increased from 20% to 25% the number of

570   herds depopulated was substantially increased and the impact of vaccination decreased. Biosecurity

571   and movement controls are known to be important aspects of a control strategy during a FMD outbreak

572   due to the potential risk of disease spread (Anderson, 2002; Cottral, 1969; Ellis-Iversen et al., 2011).

573   Additionally, identifying the personnel requirements to achieve sufficient levels of biosecurity and

574   movement controls is needed, as well as the impact on animal welfare.

575   The estimates of the probability of indirect transmission and achievable movement controls are

576   uncertain parameters, based solely on USDA subject matter expert opinion. Model outputs are quite

577   sensitive to these parameters and an improved knowledge of the efficacy of biosecurity practices and

578   the ability to achieve movement controls to limit direct and indirect transmission are necessary for

579   more focused planning of optimal control efforts.

580   The validity of results reported here are dependent on application of sufficient resources

581   required to implement the controls. Depopulation has been a mainstay of FMDV control plans however

582   the ability to depopulate large feedlots may be questionable (McReynolds et al 2014b), and further

583   modeling may be necessary to assess alternatives.

584   Finally, the results reported here do not account for the potential of a reservoir of FMDV

585   infection in the wildlife population. FMDV can infect deer and feral swine and establishment in these

586   populations could substantially complicate eradication efforts (Ward et al., 2007).

587

588   *Conclusion*

589   In this simulation study of an FMD outbreak in the central U.S., scenarios with large

590   vaccination zones had shorter median outbreak durations and fewer numbers of herds destroyed.

591   Increasing the vaccination capacity had a small impact on the outbreak and may not be feasible if

592   vaccine production and delivery is limited. In these scenarios, feedlots $\geq$3,000 head had the highest

593   vaccination priority and even with larger vaccine capacity few other production types were vaccinated

594   in some scenarios. Outbreak size and number of herds depopulated were sensitive to biosecurity

595   practices and movement controls and to a lesser extent indirect contact rates. The level of biosecurity

596   required to achieve a given probability of indirect transmission and the ability to restrict indirect

597   movement consistent with acceptable animal welfare is uncertain. Vaccination was not beneficial

598   compared to depopulation alone to control the outbreak when biosecurity and movement controls were

599   increased. A better understanding of the biosecurity changes necessary during an outbreak to attain

600   these levels is needed. The results of this study will provide information about the impacts of disease

601   control protocols which may be useful in choosing the optimal control methods to meet the goal of

602   rapid effective control and eradication. The results and impact of the control methods however may not

603   be applicable to other regions due to the variability of livestock production systems that are found in

604   different regions in the U.S.

605

612

613

614   References:

615

616   Anderson, I., 2002. Foot & mouth disease 2001: lessons to be learned inquiry report. London: The

617   Stationary Office. Available online at

618   http://webarchive.nationalarchives.gov.uk/20100807034701/http://archive.cabinetoffice.gov.uk/

619   fmd/fmd_report/report/index.htm. Last accessed March 8, 2014.

620   Bates, T. W., Carpenter, T. E., Thurmond, M. C. 2003a. Benefit-cost analysis of vaccination and

621   preemptive slaughter as a means of eradicating foot-and-mouth disease. Am. J. Vet. Res. 64:

622   805-812.

623   Bates, T. W., Thurmond M. C., Carpenter, T. E. 2003b. Results of epidemic simulation modeling to

624   evaluate strategies to control an outbreak of foot-and-mouth disease. Am. J. Vet. Res. 64: 205-

625   210.

626   Bouma, A., Elbers, A. R., Dekker, A., de Koeijer, A., Bartels, C., Vellema, P., van der Wal, P., van

627   Rooij, E. M., Pluimers, F. H., de Jong, M. C. 2003. The foot-and-mouth disease epidemic in The

628   Netherlands in 2001. Prev. Vet. Med. 57: 155-166.

629   Burrows, R., 1968. The persistence of foot-and mouth disease virus in sheep. J. Hyg. (Lond). 66: 633-

630   640.

631   Burrows, R., Mann, J. A., Garland, A. J., Greig A., Goodridge, D. 1981. The pathogenesis of natural

632   and simulated natural foot-and-mouth disease infection in cattle. J. Comp. Pathol. 91: 599-609.

633   Cottral, G. E., 1969. Persistence of foot-and-mouth disease virus in animals, their products and the

634   environment. Bulletin - Off. Int. Epizoot. 71: 549-568.

635   Cox, S.J, Burnett, P.V. 2009. Experimental evaluation of foot-and-mouth disease vaccines for

636   emergency use in ruminants and pigs: a review. Vet. Res. 40:13, DOI: 10.1051/vetres:2008051.

637   Dickey, B. F., Carpenter T. E., Bartell, S. M. 2008. Use of heterogeneous operation-specific contact

638   parameters changes predictions for foot-and-mouth disease outbreaks in complex simulation

639   models. Prev. Vet. Med. 87: 272-287.

640   Elbakidze, L., Highfield, L., Ward, M., McCarl B. A., Norby, B. 2009. Economics Analysis of

641   Mitigation Strategies for FMD Introduction in Highly Concentrated Animal Feeding Regions.

642   Applied Economic Perspectives and Policy 31: 931-950.

643   Ellis-Iversen, J., Smith, R., Gibbens, J., Sharpe, C., Dominguez, M., Cook, A. 2011. Risk factors for

644   transmission of foot-and-mouth disease during an outbreak in southern England in 2007. Vet.

645   Rec. 168: 128-128.

646   Ferguson, N. M., Donnelly, C. A., Anderson, R. M. 2001. The Foot-and-Mouth Epidemic in Great

647   Britain: Pattern of Spread and Impact of Interventions. Science 292: 1155.

648   Frey, H. C., Patil, S. R. 2002. Identification and review of sensitivity analysis methods. Risk Anal. 22:

649   553-578.

650   Garner, M., Hamilton, S. 2011. Principles of epidemiological modelling. Rev. Sci. Tech. 30: 407.

651   Gibbens, J., Wilesmith, J., Sharpe, C., Mansley, L., Michalopoulou, E., Ryan, J. Hudson, M.2001.

652   Descriptive epidemiology of the 2001 foot-and-mouth disease epidemic in Great Britain: the

653   first five months. Vet. Rec. 149: 729-743.

654   Graves, J., 1979. Foot-and mouth disease: a constant threat to US livestock. J. Am. Vet. Med. Assoc.

655   174: 174.

656   Greathouse, B. D., 2010. Vaccination Strategies for a Foot-and-Mouth Disease Outbreak in Southwest

657   Kansas, Colorado State University.

658   Harvey, N., Reeves, A.. 2010. Model description: North American Animal Disease Spread Model 3.2.

659   Harvey, N., Reeves, A., Schoenbaum, M. A., Zagmutt-Vergara, F. J., Dube, C., Hill, A. E., Corso, B. A.,

660   McNab, W. B., Cartwright, C. I., Salman, M. D. 2007. The North American Animal Disease

661   Spread Model: a simulation model to assist decision making in evaluating animal disease

662   incursions. Prev. Vet. Med. 82: 176-197.

663   Holm, S., 1979. A simple sequentially rejective multiple test procedure. Scandinavian journal of

664 statistics: 65-70.

665 Hueston, W., 1993. Assessment of national systems for the surveillance and monitoring of animal

666 health. Rev. Sci. Tech. 12: 1187-1187.

667 Hullinger P., C. Melius, S. Powers, Robertson A., Tammero, L. 2009. Wheeler R. *FMD Architecture*

668 *Analysis: Feasibility of Existing Response Plans and Evaluation of Alternatives*. Lawrence

669 Livermore National Laboratory: LLNL-TR-413989 OUO.

670 Keeling, M. J., Shattock, A. 2012. Optimal but unequitable prophylactic distribution of vaccine.

671 Epidemics 4: 78-85.

672 Keeling, M. J., Woolhouse, M. E., May, R. M., Davies, G., Grenfell, B. T. 2003. Modelling vaccination

673 strategies against foot-and-mouth disease. Nature 421: 136-142.

674 Laurence, C., 2002. Animal welfare consequences in England and Wales of the 2001 epidemic of foot

675 and mouth disease. Rev. Sci. Tech. 21: 863.

676 Mardones, F., Perez, A., Sanchez, J., Alkhamis, M., Carpenter, T. 2010. Parameterization of the

677 duration of infection stages of serotype O foot-and-mouth disease virus: an analytical review

678 and meta-analysis with application to simulation models. Vet. Rec. 41: 45.

679 McReynolds, S. W., Sanderson, M. W., Reeves, A., Hill, A. E., Sinclair, M., Salman, M. D. 2014a.

680 Direct and Indirect contact rates among livestock operations in Colorado and Kansas. J. Am.

681 Ved. Med. Assoc. 244:1066-1074.

682 McReynolds SM, Sanderson, MW. 2014b. The feasibility of methods to depopulate cattle in a large

683 feedlot during a Foot and Mouth Disease outbreak. *J. Am Vet Med Assoc*. 244:291-298.

684 Melius, C. Robertson, A., HullingerP. 2006. Developing livestock facility type information from

685 USDA agricultural census data for use in epidemiological and economic models. Department of

686 Homeland Security, Lawrence Livermore National Laboratory, UCRL-TR 226008.

687 NASS, USDA. 2007. Census of Agriculture. US Department of Agriculture, National Agricultural

688 Statistics Service, Washington, DC.

689   National Audit Office, Department of Environment, Food and Rural Affairs, 2005. Foot and Mouth

690   Disease: Applying the Lessons. www.nao.org.uk (accessed October 23, 2012).

691   NBAF, (National Bio and Agro-Defense Facility), 2012. Updated Site-Specific Biosafety and

692   Biosecurity Mitigation Risk Assessment, United Stated Department of Homeland Security.

693   Office International des Epizooties/World Organisation for Animal Health, 2013 "Foot and mouth

694   disease." Terrestrial animal health code Chapter 8.6 http://www.oie.int/en/international-

695   standard-setting/terrestrial-code/ (accessed August 28, 2013)

696   Paarlberg, P. L., Lee, J. G., Seitzinger, A. H. 2002. Potential revenue impact of an outbreak of foot-and-

697   mouth disease in the United States. J. Am. Vet. Med. Assoc. 220: 988-992.

698   Pendell, D. L., Leatherman, J. C., Schroeder, T. C., Alward, G. S. 2007. The Economic Impacts of a

699   Foot-And-Mouth Disease Outbreak: A Regional Analysis. J. Agr. Appl. Econ. 39: 19-33.

700   Perez, A. M., Ward, M. P., Carpenter, T. E. 2004. Control of a foot-and-mouth disease epidemic in

701   Argentina. Prev. Vet. Med. 65: 217-226.

702   Pluimers, F. H., 2004. Foot-and-Mouth disease control using vaccination: the Dutch experience in

703   2001. Dev Biol (Basel) 119: 41-49.

704   Premashthira, S., 2012. Uses of quantitative spatial analysis and epidemiological simulation modeling

705   for assessing control strategies for foot-and-mouth disease, Colorado State University.

706   Premashthira, S., Salman, M. D., Hill, A. E., Reich R. M., Wagner, B. A. 2011. Epidemiological

707   simulation modeling and spatial analysis for foot-and-mouth disease control strategies: a

708   comprehensive review. Anim. Health Res. Rev. 12: 225.

709   Reeves, A., 2012a "User's guide for WH: A simulation model of within-unit disease dynamics."

710   Colorado State University http://www.naadsm.org/wh (accessed June 17, 2013)

711   Reeves, A., 2012b. Construction and evaluation of epidemiologic simulation models for the within- and

712   among-unit spread and control of infectious diseases of livestock and poultry, Colorado State

713   University.

714 Salt, J., Barnett, P., Dani, P., Williams, L.1998. Emergency vaccination of pigs against foot-and-mouth

715   disease: protection against disease and reduction in contact transmission. Vaccine 16: 746-754.

716 Schroeder, TC, Pendell, DL. Sanderson, MW. McReynolds SM. Economic Impact of Alternative FMD

717   Emergency Vaccination Strategies in the Midwestern United States. Accepted, *Journal of*

718   *Agricultural and Applied Economics*

719 Schoenbaum, M. A., Disney, W. T. 2003. Modeling alternative mitigation strategies for a hypothetical

720   outbreak of foot-and-mouth disease in the United States. Prev. Vet. Med. 58: 25-52.

721 StataCorp. 2011. Stata: Release 12. Statistical Software College Station, TX, StataCorp LP.

722 Sutmoller, P., Barteling, S. S., Olascoaga R. C., Sumption, K. J. 2003. Control and eradication of foot-

723   and-mouth disease. Virus Res. 91: 101-144.

724 Volkova, V. V., Bessell, P. R., Woolhouse, M. E., Savill, N. J. 2011. Evaluation of risks of foot-and-

725   mouth disease in Scotland to assist with decision making during the 2007 outbreak in the UK.

726   Vet. Rec. 169: 124.

727 Ward, M. P., Highfield, L. D., Vongseng, P., Graeme Garner, M. 2009. Simulation of foot-and-mouth

728   disease spread within an integrated livestock system in Texas, USA. Prev. Vet. Med. 88: 286-

729   297.

730 Ward, M. P., Laffan, S. W. Highfield. L. D. 2007. The potential role of wild and feral animals as

731   reservoirs of foot-and-mouth disease. Prev. Vet. Med. 80: 9-23.

732 Woolhouse, M., Donaldson, A. 2001. Managing foot-and-mouth. Nature 410: 515-516.

733 Yang, P. C., Chu, R. M., Chung, W. B., Sung, H. T. 1999. Epidemiological characteristics and financial

734   costs of the 1997 foot-and-mouth disease epidemic in Taiwan. Vet. Rec. 145: 731-734.

735 Yoon, H., Wee, S. H., Stevenson, M. A., O'Leary, B. D., Morris, R. S., Hwang, I. J., Park, C. K., Stern,

736   M. W. 2006. Simulation analyses to evaluate alternative control strategies for the 2002 foot-and-

737   mouth disease outbreak in the Republic of Korea. Prev. Vet. Med. 74: 212-225.

738

Table 1. Simulation population of the 8-state region in the central U.S. that was used in

NAADSM with the number of animals and herds by production type.

Production Type	Animals	Herds
Cow-calf	9,698,630	86,655
Feedlot-Large (≥3,000 head)	9,147,279	979
Feedlot-Small (<3,000 head)	7,377,698	25,096
Dairy	1,062,276	3,232
Swine-Large (≥1,000 head)	9,227,569	1,071
Swine-Small (<1,000 head)	663,465	6,463
Beef-swine mix	520,283	5,159
Sheep	1,716,028	22,965
Total	39,413,228	151,620

Table 2. Description of vaccination strategy for 17 simulated scenarios of a potential foot and mouth disease virus outbreak in a central region of the U.S.

Scenario	Large Feedlots Vaccination [b]	Vaccination Capacity [c]	Vaccination Trigger (herds)	Size of Vaccination Zone (km)
1[a]	-	-	-	-
2	Priority	5,10	10	10
3	Only	1,3	10	10
4	Priority	5,10	10	50
5	Only	1,3	10	50
6	Priority	50,80	100	10
7	Only	8,15	100	10
8	Priority	50,80	100	50
9	Only	8,15	100	50
10	Priority	5,10	100	10
11	Only	1,3	100	10
12	Priority	5,10	100	50
13	Only	1,3	100	50
14	Priority	50,80	10	10
15	Only	8,15	10	10
16	Priority	50,80	10	50
17	Only	8,15	10	50

[a] Scenario 1 baseline depopulation without vaccination

[b] Priority – from highest to lowest: large feedlot (≥3,000 head), small feedlot (<3,000 head), large swine (≥1,000 head), small swine (<1,000 head), beef-swine, dairy, cow-calf, and small ruminant.

Only – Large feedlots only vaccinated.

[c] The capacity for vaccination protocols in number of herds per day by 22 days after disease detection and by 40 days after disease detection

Table 3. Median duration of outbreak, number of herds depopulated, number of animals depopulated, number of herds vaccinated, and number of animals vaccinated for each scenario $(10^{th} - 90^{th}$ percentiles) [rank most to least optimal] of a potential foot and mouth disease virus outbreak in a central region of the U.S.

Scenario	Outbreak Duration (days)	Number of Herds Depopulated	Number of Animals Depopulated (1000)	Number of Herds Vaccinated	Number of Animals Vaccinated (1000)
1	527[f] (87-621)	6,890[h] (32-8,101) [17]	13,663 (196-17,611)		
2	608[i] (102-767)	2,227[g] (42-2,449) [13]	9,921 (222-10,600)	5,709[i] (657-7304)	7,644 (0-8,500)
3	530[fg] (48-687)	2,248[g] (10-3,156) [11]	9,939 (72-11,500)	472[b] (0-514) [3]	4,319 (0-4,764)
4	223[b] (86-310)	416[b] (31-879) [2]	1,736 (238-3,214)	1,876[g] (494-2,736)	16,400 (1,490-
5	389[e] (286-559)	1,735[e] (1,326-2,063)	7,508 (5,774-8,591)	1,043[e] (725-1,460) [6]	10,300 (7,000-
6	459[fg] (45-721)	1,991[f] (9-2,301) [9]	9,098 (65-10,000)	30,594[k] (0-51,136) [15]	19,600 (0-23,832)
7	550[ghi] (64-753)	2,249[g] (15-5,133) [15]	10,000 (81-12,500)	458[b] (0-488) [2]	4,183 (0-4,600)
8	202[ab] (131-390)	440[b] (233-616) [3]	1,863 (1,071-2,395)	10,000[j] (6,400-24,560)	14,900 (10,000-
9	342[d] (256-528)	1,605[d] (1,242-3,712)	6,950 (5,600-10,400)	1,044[e] (784-1,398) [7]	10,400 (7,400-
10	596[hi] (154-800)	2,203[g] (49-3,270) [12]	9,968 (341-11,121)	5,165[h] (0-7,030) [11]	7,132 (0-8,330)

11	540 [fgh] (90-709)	2,276 [g] (32-7,318) [16]	10,000 (268-15,000)	425 [a] (0-463) [1]	3,851 (0-4,263)
12	250 [c] (146-318)	855 [c] (234-1,150) [5]	3,702 (968-4,727)	1,800 [g] (635-2,420) [9]	17,200 (6,250-
13	369 [de] (244-579)	1,848 [f] (1,320-7,904)	8,008 (6,275-16,360)	859 [d] (528-1,098) [5]	8,461 (4,833-11,000)
14	527 [fghi] (77-791)	1,925 [f] (22-2,174) [8]	9,098 (141-10,000)	37,928 [l] (746-59,380)	21,600 (205-25,800)
15	545 [fgh] (363-706)	2,238 [g] (1,681-2,648)	9,922 (8,017-10,675)	499 [c] (432-525) [4]	4,561 (3,850-4,860)
16	181 [a] (123-366)	252 [a] (107-427) [1]	1,028 (515-1,644)	11,902 [j] (6,923-26,654)	15,500 (10,000-
17	241 [bc] (133-568)	440 [b] (87-850) [4]	1,754 (521-3,373)	1,329 [f] (528-2,718) [8]	13,100 (5,000-

Values within columns with different superscripts are different p<0.05 (adjusted p-value

accounting for multiple comparisons)

Table 4. The top 5 rankings of the scenarios with the lowest number of herds depopulated and shortest outbreak duration of a potential foot and mouth disease virus outbreak in a central region of the U.S. Rankings based on a Kruskal-Wallis one-way analysis of variance.

Sensitivity Analysis Parameter	Lowest number of herds depopulated					Shortest outbreak duration				
Rank	1	2	3	4	5	1	2	3	4	5
Baseline Scenarios	16	4	8	17	12	16	4	8	12	17
Indirect Transmission 15%	17	16	4	10	6	17	16	4	8	10
Indirect Transmission 25%	16	8	4	17	1	4	1	11	16	3
Indirect Movement Control 40% of baseline	16	8	1	4	17	1	17	11	4	3
Indirect Movement Control 20% of baseline	16	4	17	8	1	16	4	17	8	7
Indirect Contact Rate -20%	16	4	17	8	12	16	4	17	8	12
Indirect Contact Rate +20%	16	8	4	17	1	4	16	7	1	11

Appendix 1. Disease state and spread parameters

Table A1. Calculated mean daily direct contact rates per herd used to parameterize the

NAADSM model based on livestock contact survey results in Colorado and Kansas.

Source Production Type	Destination Production Type	Mean Number of Contacts per Day per Herd	Movement distance in km
Cow/Calf	Cow/Calf	0.027	Exponential (116.88)
Cow/Calf	Large Feedlot	0.002	Weibull (1.35,344.40)
Cow/Calf	Small Feedlot	0.002	Weibull (1.35,344.40)
Cow/Calf	Beef/Swine	0.027	BetaPERT (1.60,80.50,241.40)
Dairy	Dairy	0.065	Pearson 5 (1.01,7.73)
Large Feedlot	Large Feedlot	0.005	Gamma (6.87,71.25)
Large Swine	Large Swine	0.186	LogLogistic (1.10,66.10,1.24)
Small Feedlot	Large Feedlot	0.019	Weibull (1.46,547.06)
Small Feedlot	Small Feedlot	0.017	Beta (8.04,33.76,0.00,2643.80)
Small Swine	Small Swine	0.013	BetaPERT (0,20,181)
Small Swine	Beef/Swine	0.013	Lognormal (166.74,748.64)
Beef/Swine	Cow/Calf	0.027	Exponential (116.68)
Beef/Swine	Large Feedlot	0.003	Weibull (1.35,344.40)
Beef/Swine	Small Feedlot	0.003	Weibull (1.35,344.40)
Beef/Swine	Beef/Swine	0.026	Lognormal (166.74,748.64)
Beef/Swine	Small Swine	0.013	Lognormal (166.74,748.64)
Small Ruminant	Small Ruminant	0.024	Exponential (116.88)

[a]All combinations that are not listed above had a mean daily contact rate of 0.

[b]Beta distribution is a continuous distribution defined by four parameters: $\alpha1$, $\alpha2$, a minimum

value, and a maximum value.

Table A2. Calculated mean daily indirect contact rate (per herd per day) by production type used to parameterize the NAADSM model based on livestock contact survey results in Colorado and Kansas.

	FROM							
TO	Cow/Calf	Small Feedlot	Large Feedlot	Dairy	Small Swine	Large Swine	Small Ruminant	Beef/Swine
Cow/Calf	0.133	0.090	0.123	0.181	0.005	0.026	0.018	0.009
Small Feedlot	0.141	0.095	0.131	0.191	0.005	0.028	0.019	0.009
Large Feedlot	1.711	1.155	1.589	2.326	0.063	0.337	0.229	0.114
Dairy	0.623	0.420	0.578	1.045	0.026	0.136	0.093	0.041
Small Swine	0.020	0.014	0.019	0.030	0.003	0.014	0.003	0.003
Large Swine	0.044	0.030	0.041	0.066	0.015	0.086	0.015	0.013
Small Ruminant	0.052	0.035	0.048	0.078	0.002	0.008	0.070	0.001
Beef/Swine	0.092	0.062	0.086	0.125	0.007	0.033	0.012	0.006

Table A3. Distance distributions of indirect contacts

Production type of movement source	Movement distance in km for indirect contacts
Cow/calf	Beta (8.39,18.78,0.00,887.39)
Dairy	Beta (7.41,8.86,0.00,1580.40)
Large feedlots	Gamma (6.87,71.25)
Small feedlots	Beta (8.04,13.76,0.00,2463.80)
Large swine	Beta (4.55,4.35,0.00,1143.80)
Small swine	Beta (4.42,4.19,0.00,1167.00)
Beef/swine	Beta (5.48,14.55,0.00,791.36)
Small ruminants	Beta (5.21,4.26,0.00,332.66)

[a]Beta distribution is a continuous distribution defined by four parameters: $\alpha 1$, $\alpha 2$, a minimum value, and a maximum value.

Table A4. Defining the duration of the *disease state* periods in days by production type[a]

Production type	Duration of the *latent period*	Duration of the *subclinical, infectious period*	Duration of the *clinical, infectious period*	Duration of the *immune period*
Cow/calf	Neg. binomial (12,0.77)	Poisson (1.77)	Gamma (35.94,0.65)	Gaussian (1095, 180)
Dairy	Neg. binomial (20,0.85)	Poisson (1.74)	Gamma (26.72,1.03)	Gaussian (1095, 180)
Large feedlots	Neg. binomial (26,0.87)	Binomial (9,0.19)	Gamma (170.51,0.23)	Gaussian (1095, 180)
Small feedlots	Neg. binomial (16,0.82)	Poisson (1.70)	Gamma (48.01,0.58)	Gaussian (1095, 180)
Large swine	Neg. biniomial (4, 0.58)	Poisson (2.05)	Gamma (81.90,0.49)	Weibull (5, 985)
Small swine and beef/swine	Neg. biniomial (4, 0.56)	Poisson (2.10)	Gamma (12.78,1.66)	Weibull (5, 985)
Small ruminants	Neg. biniomial (14, 0.74)	Neg. binomial (14,0.85)	Gamma (15.78,1.22)	Gaussian (930, 90)

[a] from Mardones et. al., 2010 see text for details.

Figure 1. An 8-state outlined region of central U.S. selected for modeling the potential of a foot and mouth disease outbreak initiated in a large feedlot in Northeast Colorado.

Figure 2. Median number of new herds detected as clinically infected by week of a potential foot and mouth disease virus outbreak in a central region of the U.S.
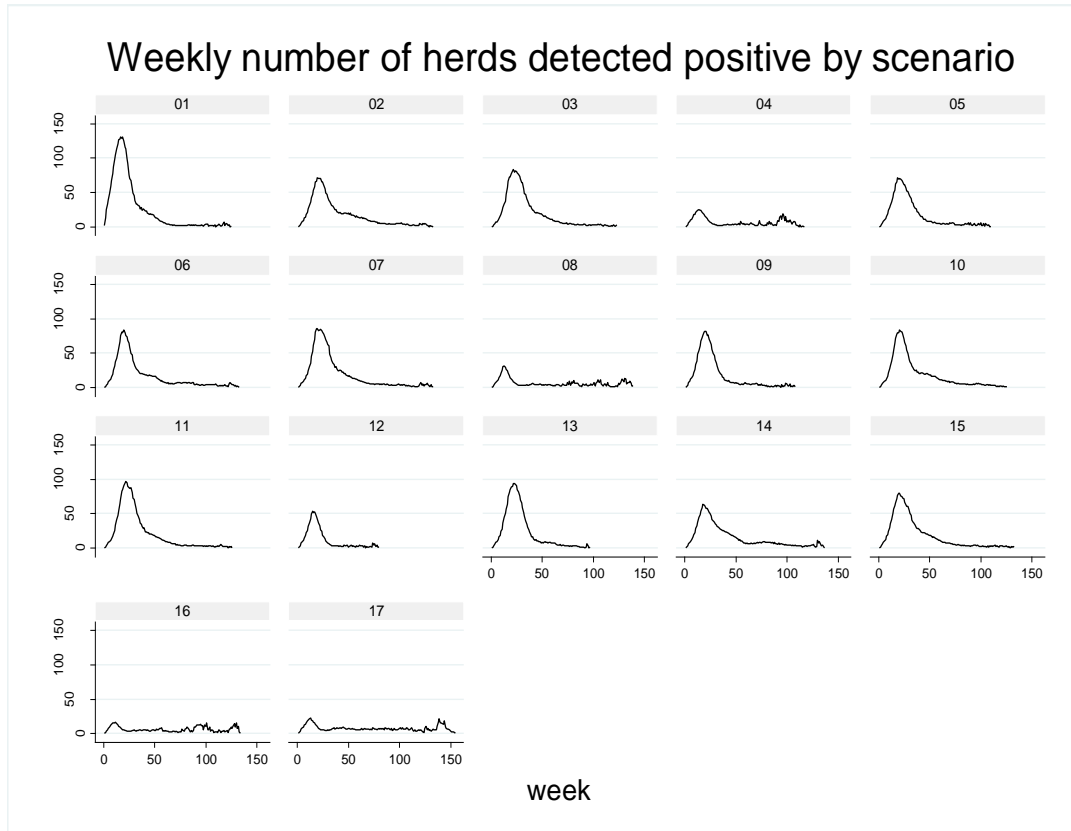
Figure 3. The total number of animals vaccinated each week by scenario number of a potential

foot and mouth disease virus outbreak in a central region of the U.S.

Weekly number of animals vaccinated by scenario
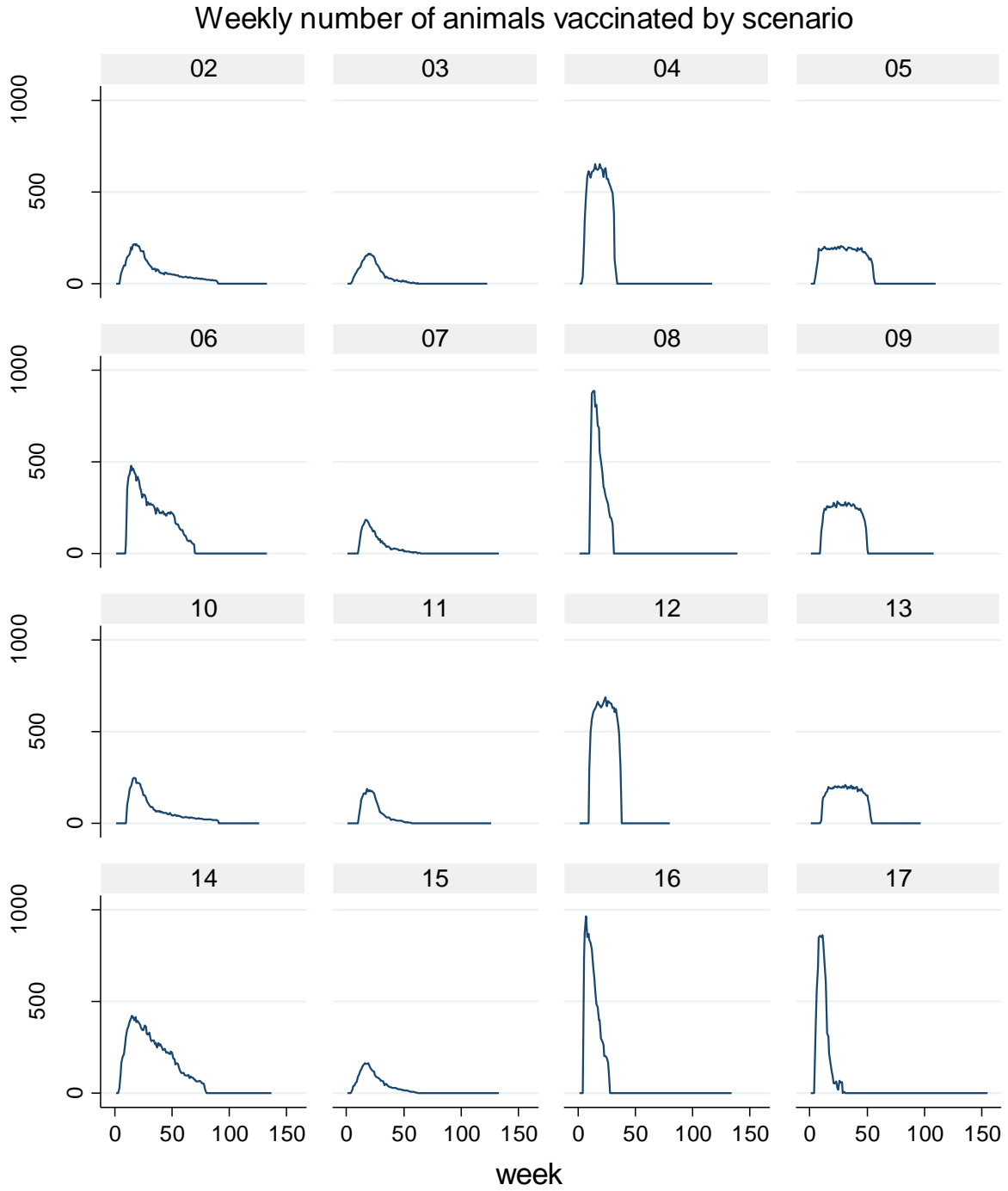
Figure 4. Box plots of the duration of the active disease phase for the sensitivity analysis of the probability of transmission given indirect contact is at 15%, 20%, and 25% for all scenarios of a potential foot and mouth disease virus outbreak in a central region of the U.S.
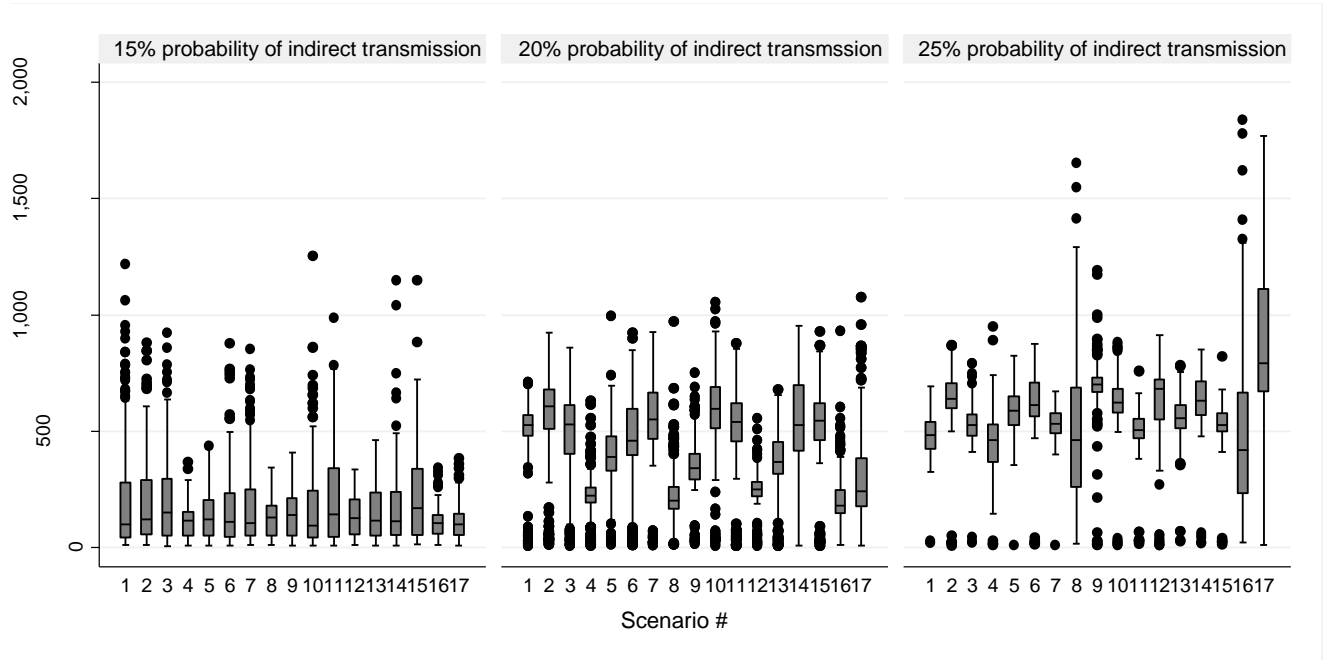
[a]The box plot parameters are boxes at 25th and 75th percentiles, the line in the box is the median, whiskers are 5th and 95th percentiles and dots are outliers.
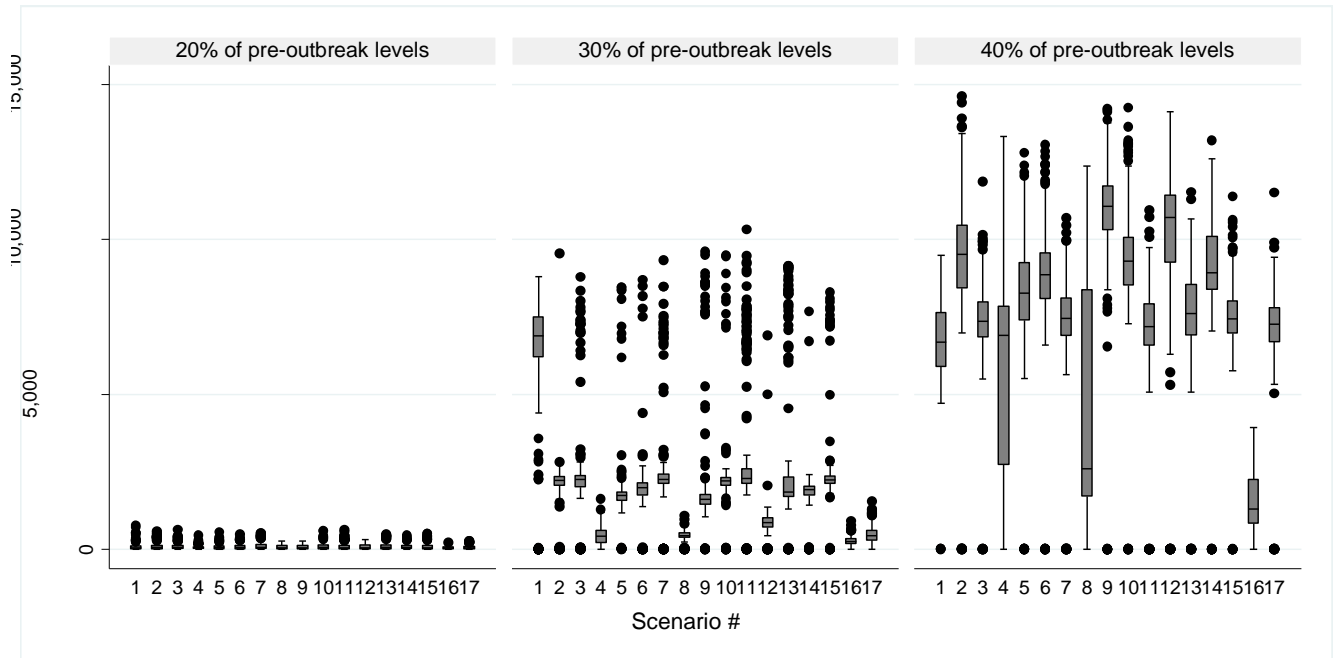
Figure 5. Box plots of the number of herds depopulated for the sensitivity analysis of the

probability of transmission given indirect contact at 15%, 20%, and 25% for all scenarios of a

potential foot and mouth disease virus outbreak in a central region of the U.S.
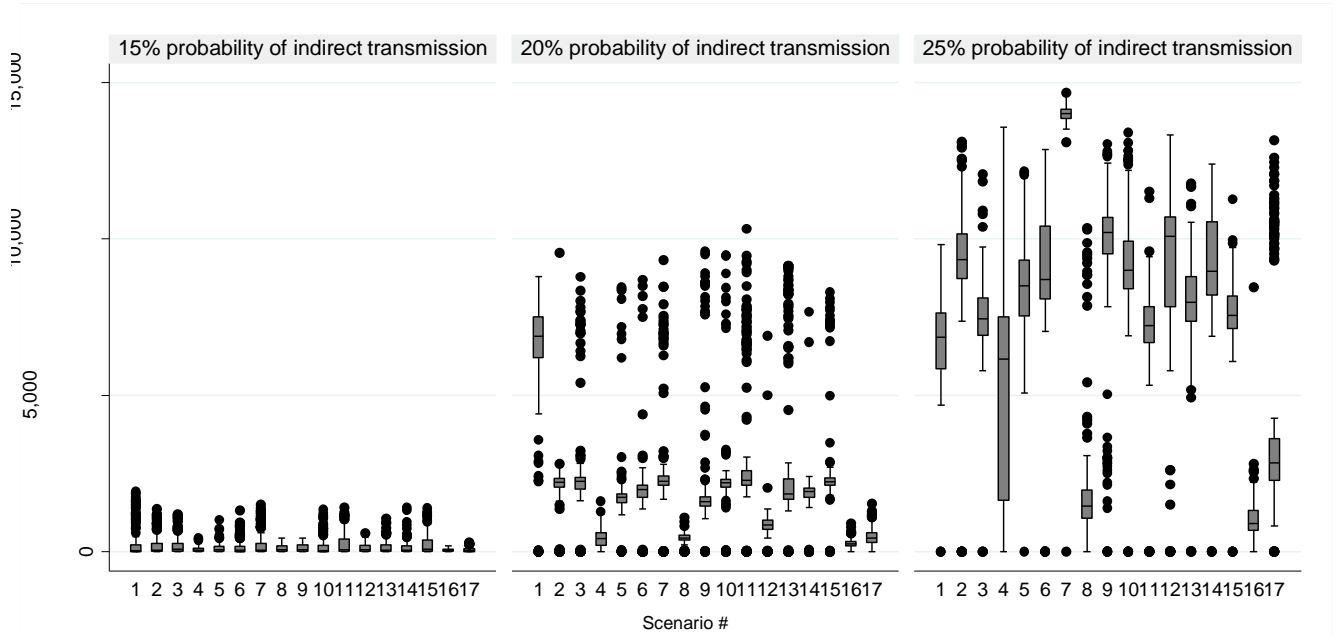
[a]The box plot parameters are boxes at 25th and 75th percentiles, the line in the box is the median, whiskers are 5th and

95th percentiles and dots are outliers.

Figure 6. Box plots of the number of vaccinated herds for the sensitivity analysis of the

probability of transmission given indirect contact is at 15%, 20%, and 25% for all scenarios of a

potential foot and mouth disease virus outbreak in a central region of the U.S.
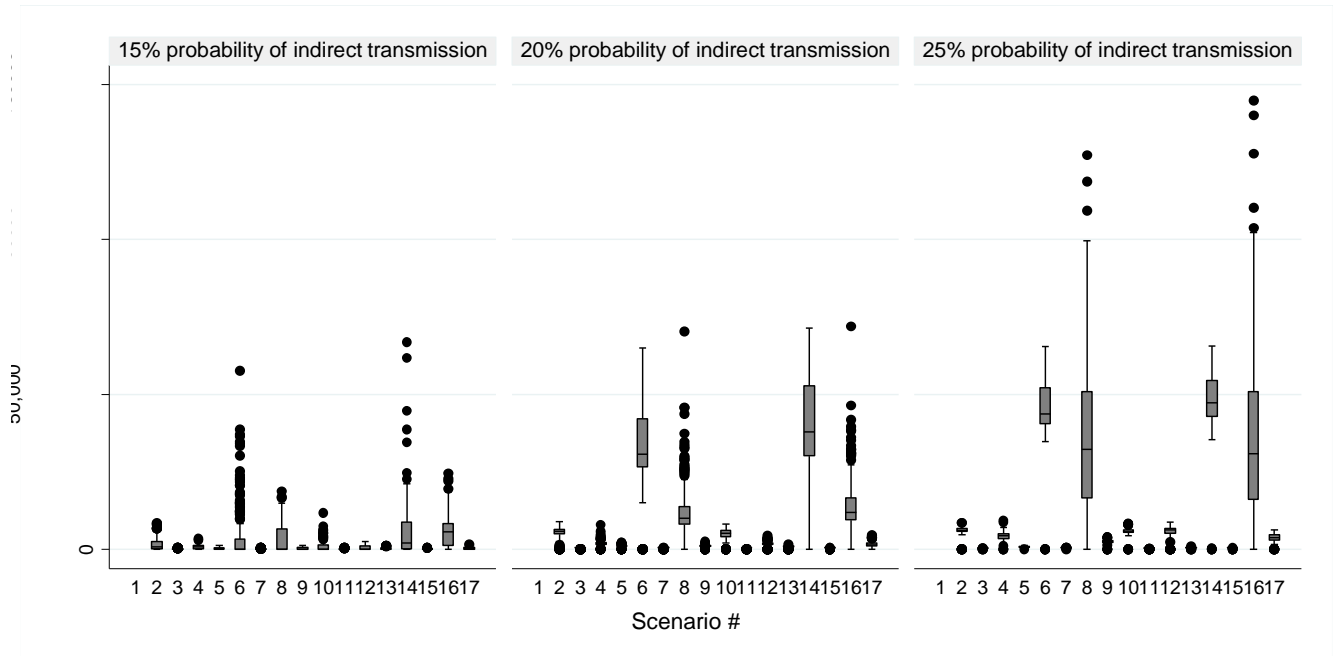
[a]The box plot parameters are boxes at 25th and 75th percentiles, the line in the box is the median, whiskers are 5th and
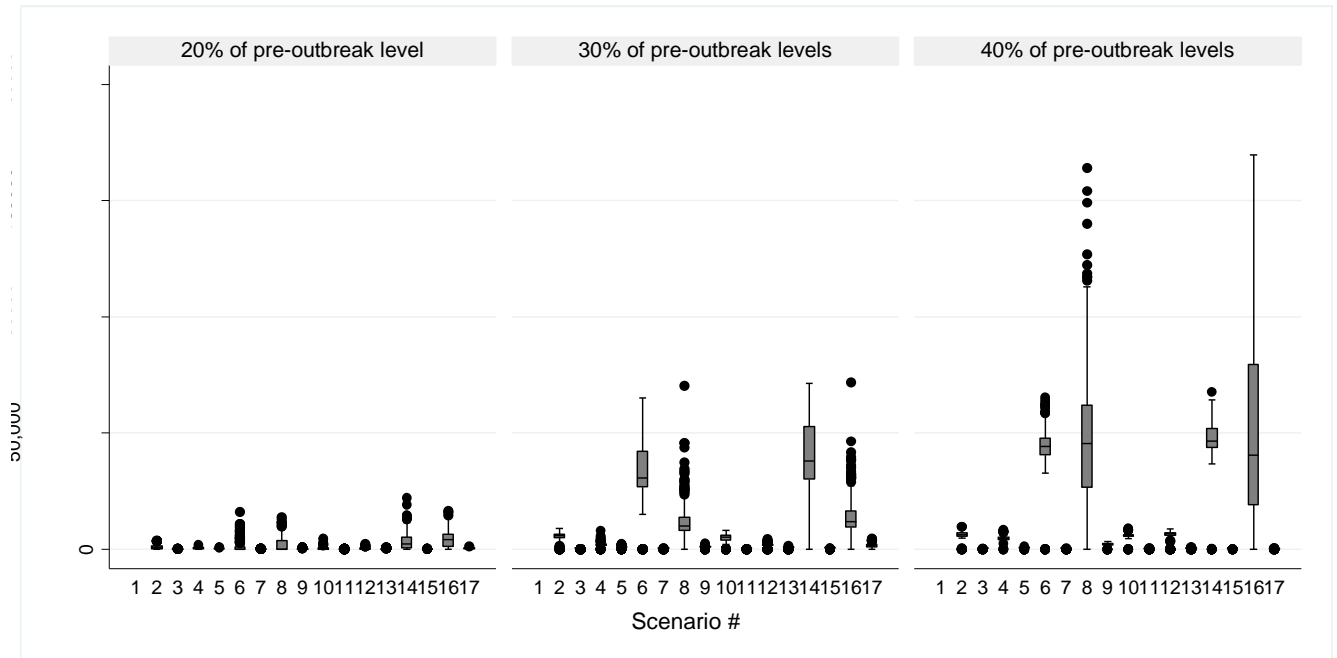
95th percentiles and dots are outliers.

Figure 7. Box plots of the duration of the active disease phase for the sensitivity analysis of the movement controls at 20%, 30%, and 40% of pre-outbreak levels for all scenarios of a potential foot and mouth disease virus outbreak in a central region of the U.S.
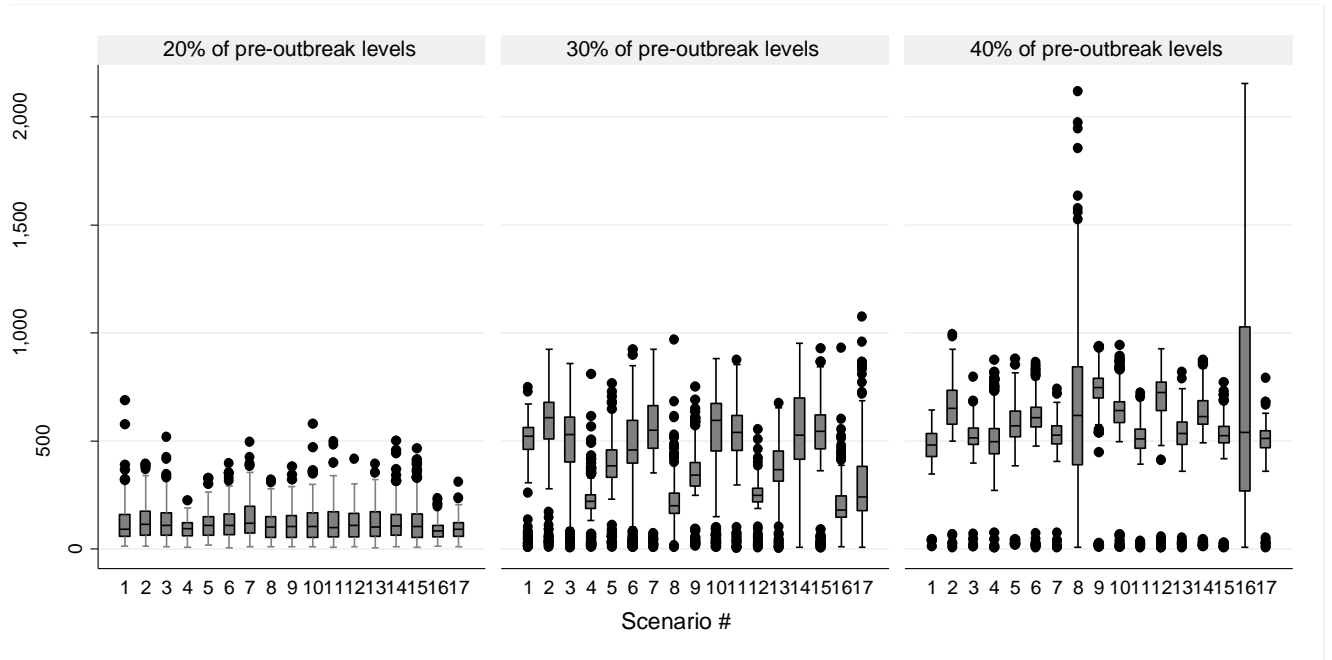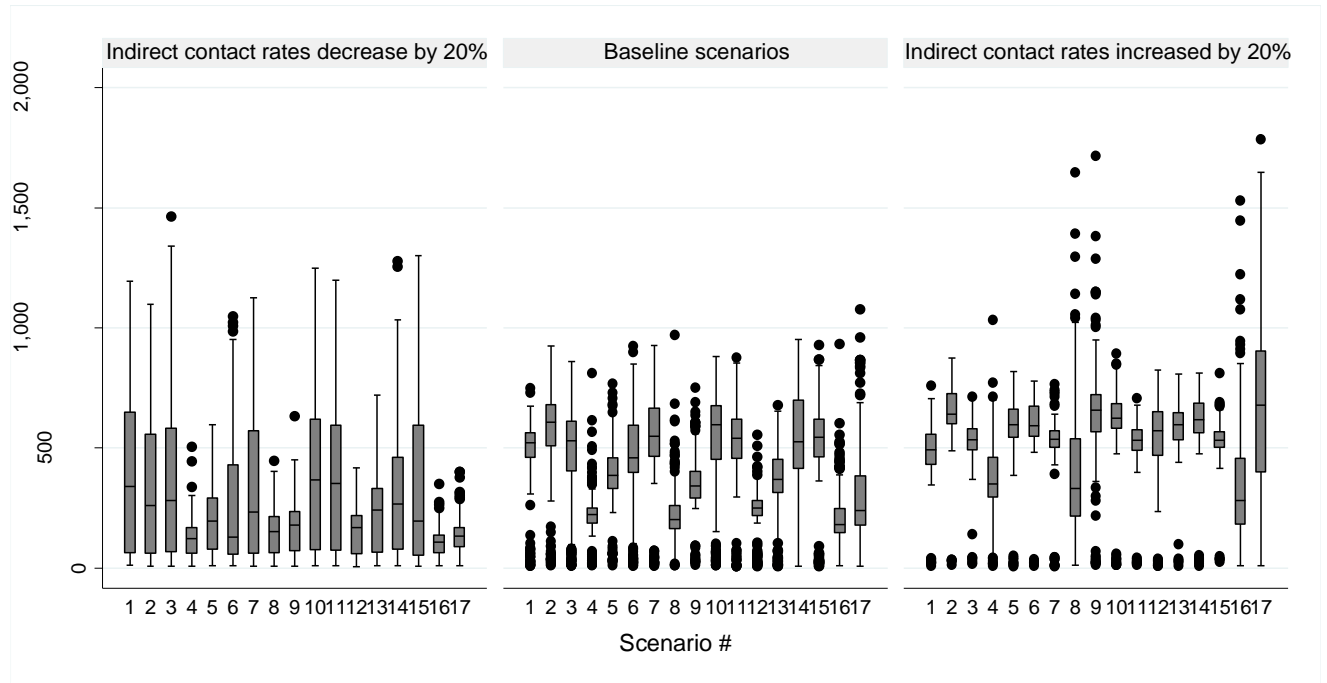

[a]The box plot parameters are boxes at 25th and 75th percentiles, the line in the box is the median, whiskers are 5th and 95th percentiles and dots are outliers.

Figure 8. Box plots of number of herds depopulated for the sensitivity analysis of the movement

controls at 20%, 30%, and 40% of pre-outbreak levels for all scenarios of a potential foot and

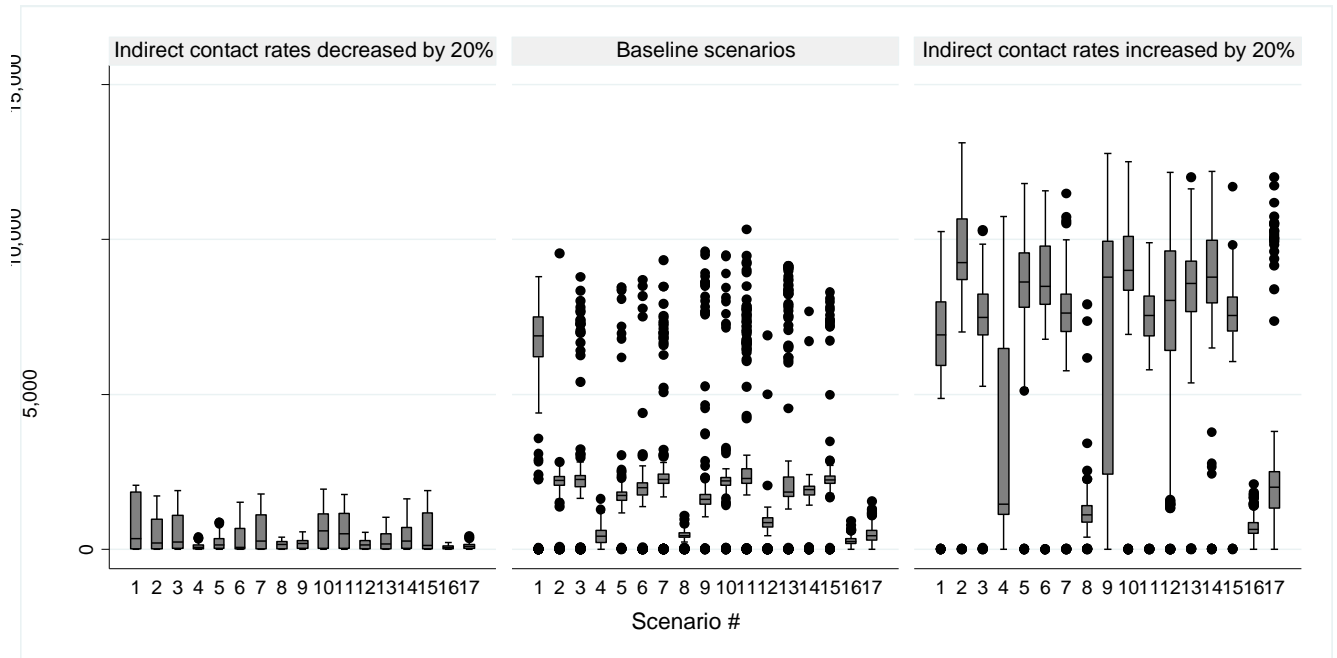mouth disease virus outbreak in a central region of the U.S.

[a]The box plot parameters are boxes at 25th and 75th percentiles, the line in the box is the median, whiskers are 5th and

95th percentiles and dots are outliers.

Figure 9. Box plots of number of herds vaccinated for the sensitivity analysis of the indirect movement controls at 20%, 30%, and 40% of pre-outbreak levels for all scenarios of a potential foot and mouth disease virus outbreak in a central region of the U.S.

[a]The box plot parameters are boxes at 25th and 75th percentiles, the line in the box is the median, whiskers are 5th and 95th percentiles and dots are outliers.

Figure 10. Box plots of the duration of the active disease phase for the sensitivity analysis of the

indirect contact rate and the baseline indirect contact rate for all scenarios of a potential foot and

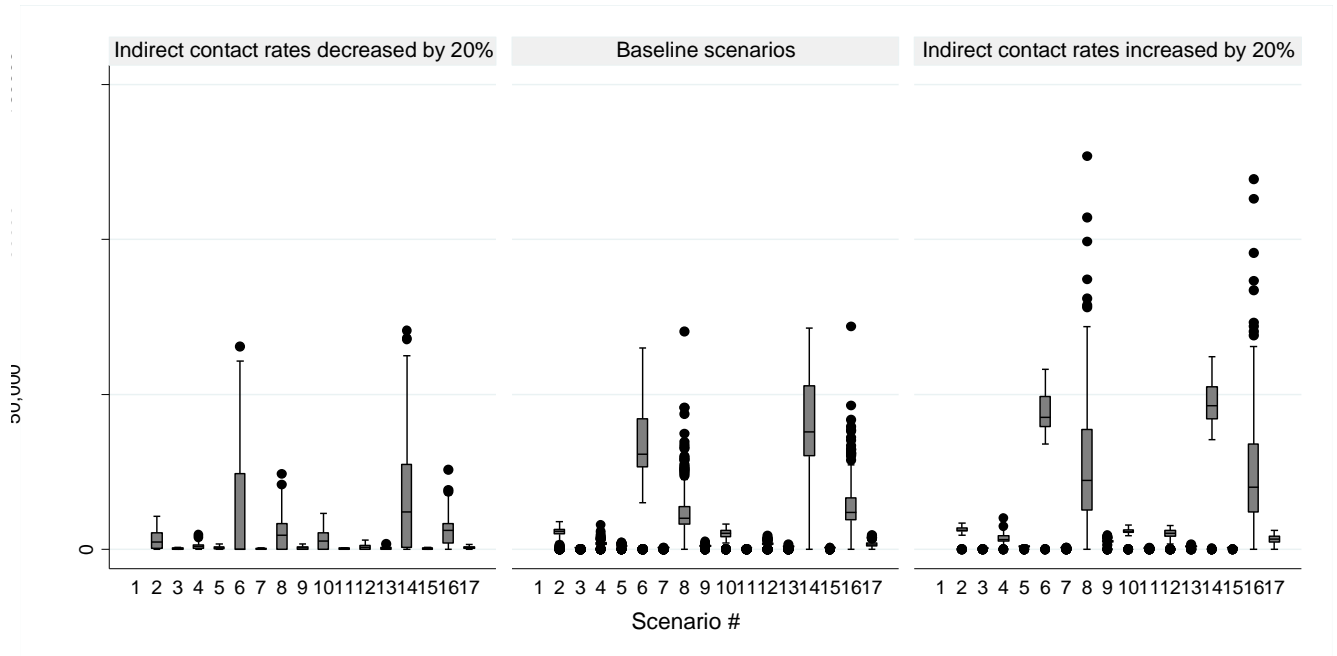mouth disease virus outbreak in a central region of the U.S.

[a]The box plot parameters are boxes at 25th and 75th percentiles, the line in the box is the median, whiskers are 5th and

95th percentiles and dots are outliers.

Figure 11. Box plots of the number of herds depopulated for the sensitivity analysis of the

indirect contact rate and the baseline indirect contact rate for all scenarios of a potential foot and

mouth disease virus outbreak in a central region of the U.S.

[a]The box plot parameters are boxes at 25th and 75th percentiles, the line in the box is the median, whiskers are 5th and

95th percentiles and dots are outliers.

Figure 12. Box plots of the number of herds vaccinated for the sensitivity analysis of the indirect

contact rate and the baseline indirect contact rate for all scenarios of a potential foot and mouth

disease virus outbreak in a central region of the U.S.

[a]The box plot parameters are boxes at 25th and 75th percentiles, the line in the box is the median, whiskers are 5th and

95th percentiles and dots are outliers.