Post-outbreak African horse sickness surveillance: A scenario tree evaluation in South Africa's controlled area

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Abstract

An African horse sickness (AHS) outbreak occurred in March and April 2016 in the controlled area of South Africa. This extended an existing trade suspension of live equids from South Africa to the European Union. In the post-outbreak period ongoing passive and active surveillance, the latter in the form of monthly sentinel surveillance and a stand-alone freedom from disease survey in March 2017, took place. We describe a stochastic scenario tree analysis of these surveillance components for 24 months, starting July 2016, in three distinct geographic areas of the controlled area. Given that AHS was not detected, the probability of being free from AHS was between 98.3% - 99.8% assuming that, if it were present, it would have a prevalence of at least one infected animal in 1% of herds. This high level of freedom probability had been attained in all three areas within the first 9 months of the two–year period. The primary driver of surveillance outcomes was the passive surveillance component. Active surveillance components contributed minimally (less than 0.2%) to the final probability of freedom. Sensitivity analysis showed that the probability of infected horses showing clinical signs was an important parameter influencing the system surveillance sensitivity. The monthly probability of disease introduction needed to be increased to 20% and greater to decrease the overall probability of freedom to below 90%. Current global standards require a two-year post-incursion period of AHS freedom before re-evaluation of free zone status. Our findings show that the length of this period could be decreased if adequately sensitive surveillance is performed. In order to comply with international standards, active surveillance will remain a component of AHS surveillance in South Africa. Passive surveillance, however, can provide substantial evidence supporting

AHS freedom status declarations, and further investment in this surveillance activity would be beneficial.

Keywords

African horse sickness; Surveillance evaluation; Freedom from disease; Scenario tree

1. Introduction

African horse sickness (AHS) is a disease of equids caused by African horse sickness virus (AHSV), an *Orbivirus* transmitted by *Culicoides* midges (Coetzer & Guthrie, 2004). It is a disease of global importance and is one of six diseases for which official World Organisation for Animal Health (OIE) freedom can be obtained (OIE, 2018). The disease impacts the ability of countries to trade live equids. Notably AHS is one of six equine diseases that require above-standard biosecurity to comply with conditions for the movement of high-health high-performance (HHP) horses within international guidelines (OIE, 2016a, 2016b). There has been recent evidence of the changing distribution of several *Orbiviruses* transmitted by *Culicoides* midges. Recent large scale orbiviral epidemics, such as Bluetongue in Europe, has resulted in sensitisation to the reality that the emergence of these diseases is possible in previously unaffected regions. This is particularly true in regions that have resident vectors (MacLachlan & Guthrie, 2010; Mellor & Leake, 2000).

Historically South Africa's primary export route for live horses has relied on direct export to the European Union (EU) under existing trade protocols based on three primary import standards (EC, 2008, 2010, 2018) or through the use of Mauritius as a stepping stone to Europe (Grewar, 2016). South Africa has not directly traded domestic equines with any non-

African country since 2011 as a result of an AHS outbreak in that year (Grewar et al., 2013). South Africa does not have official OIE freedom status from AHS but does have a controlled area that is considered free from the disease which has been developed specifically for trade purposes (Bosman, Brückner, & Faul, 1995; Animal Diseases Act (Act No.35, 1984)). Sporadic outbreaks have however occurred in the controlled area and surveillance plays a crucial role in the ability to adhere to existing trade conditions. The objective of surveillance for AHS in this context is to demonstrate freedom from AHS. In this study, we aim to estimate the sensitivity and probability of freedom in the AHS controlled area throughout the two years following the 2016 outbreak (Grewar et al., 2019b). This outbreak was resolved in June 2016 and for this evaluation the first surveillance period is July 2016.

While collectively evaluating three different components of surveillance (passive surveillance, ongoing active sentinel surveillance and a structured stand-alone freedom from disease survey) we also evaluate them individually to provide a basis for justification of ongoing investment in these components. Furthermore, we provide a basis for discussion regarding the applicability of a two-year suspensive condition for a disease such as AHS in the post-outbreak period, as required by the EU and OIE (EC, 2010; OIE 2016b, 2018), assuming a well-developed surveillance program is in place.

2. Materials and Methods

2.1 Model overview and general methods

A stochastic scenario tree model was developed based on the work described by Martin et al (Martin, Cameron, & Greiner, 2007). Scenario trees in surveillance characterise a

population (in this case by geographic location) and sequentially model the infection probabilities and detection occurrences within surveillance components to give realistic estimates of outcomes such as the sensitivity of surveillance and probability of freedom. The methodology of Martin et al. (2007) establishes surveillance component sensitivity and the subsequent probability of freedom from disease accounting for multiple surveillance components. Since a reliable individual animal dataset was available, methods were modified using the hypergeometric approximation for estimating herd and component sensitivities (MacDiarmid, 1988). Sensitivity and probability of freedom outputs are reported as median probabilities with 95% probability intervals (PI) following 10000 iterations. The individual animal was considered the primary surveillance unit and the data were aggregated on a monthly basis for analysis (surveillance period).

All data were managed in a PostgreSQL database (https://postgresql.org) and the model was run in R (R Core Team, 2019) using the following packages: mc2d for management of probability distributions and Monte-Carlo simulations (Pouillot & Delignette-Muller, 2010); RPostgreSQL for data import (Conway, Eddelbuettel, Nishiyama, Prayaga, & Tiffin, 2016); dplyr, tibble and reshape2 for data manipulation (Müller & Wickham, 2018; Wickham, 2007; Wickham & Francois, 2015); functions extracted from the RSurveillance package for posterior probability of freedom calculations (Sergeant, 2016); and ggplot2 for graphical outputs (Wickham, 2009). qGIS (https://qgis.org) and PostGIS (https://postgis.net/) were used for generating spatial outputs.

2.2 Surveillance evaluation areas

African horse sickness is a legally controlled disease in South Africa and part of the control is through regionalisation of the country into AHS zones (Bosman et al., 1995; Animal Diseases Act (Act No.35, 1984)). The AHS controlled area consists of three zones – an inner AHS free zone (FZ), middle surveillance zone (SZ) and outer protection zone (PZ) - Figure 1. In practice, the FZ and SZ have the same AHS surveillance policy and they were merged for this evaluation (FZSZ). The 2016 AHS outbreak secondary containment zone, however, delineated the region where a structured freedom from disease survey was performed (Grewar et al., 2019a) and the combined FZSZ was separated into that part intersecting with the 2016 AHS secondary containment zone (FZSZ_CZ – A1 in Figure 1) and the remainder (FZSZ_NonCZ – A2 in Figure 1). The AHS PZ is considered the third surveillance area (B in Figure 1).

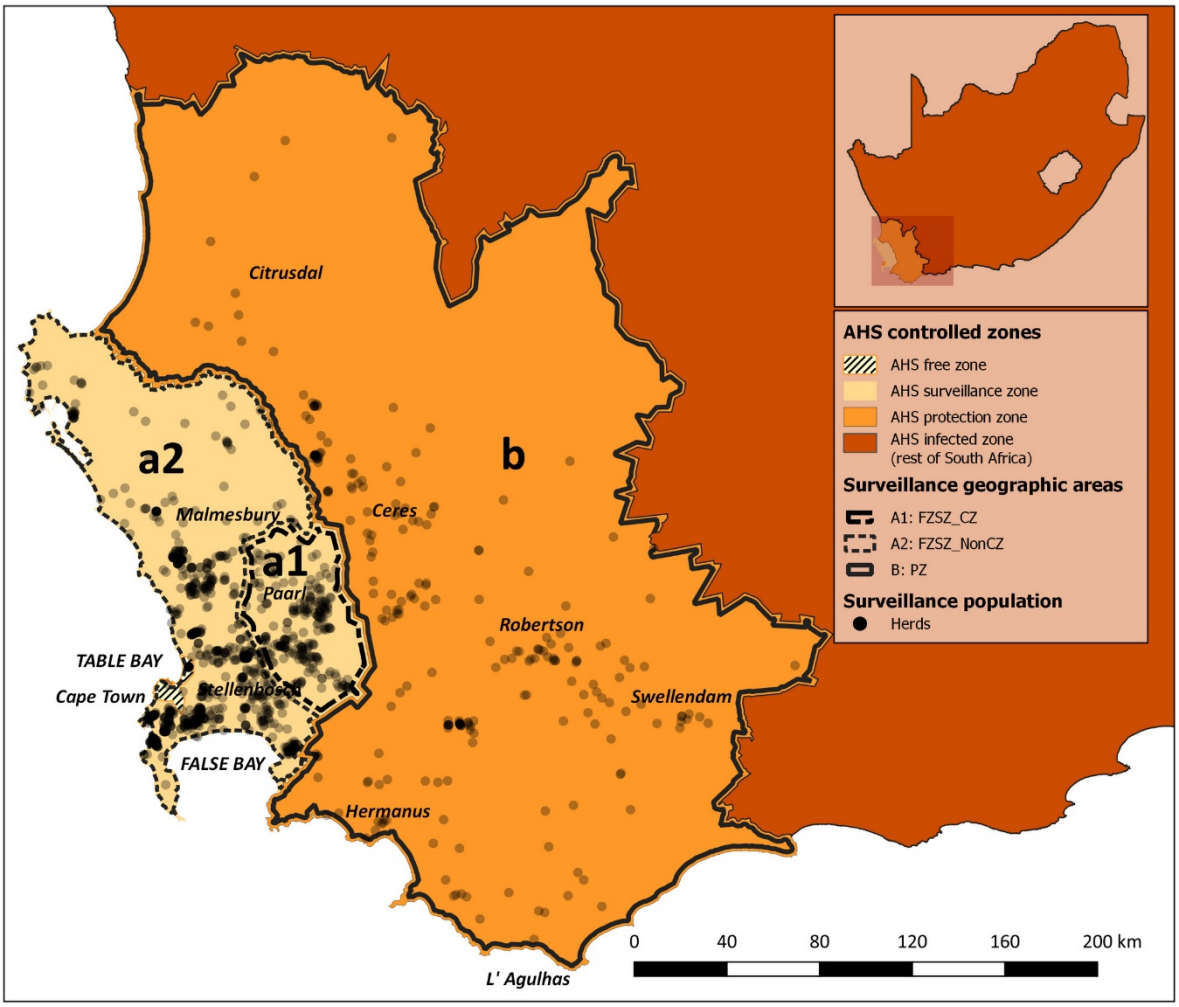

Figure 1

Surveillance evaluation areas categorising African horse sickness (AHS) surveillance evaluation. The evaluation areas are superimposed on the current South African AHS controlled zones. Evaluation area A1:FZSZ_CZ refers to the area within the AHS free and surveillance zone that includes the containment zone of the 2016 AHS outbreak (Grewar et al., 2019b); A2:FZSZ_NonCZ is that part of the AHS free and surveillance zone excluding the 2016 AHS outbreak containment zone and B: PZ reflects the boundaries of the AHS protection zone. Herds associated with surveillance are shown as black circles.

2.3 Surveillance component overview and available data

Surveillance components are defined by the source of data and the methods used for its collection to investigate the occurrence of one or more hazards in a specific population (RISKSUR consortium, 2013). We describe the evaluation of AHS in terms of three components; ongoing passive surveillance (PSC), ongoing monthly sentinel surveillance (SSC)

and a stand-alone post-outbreak freedom from AHS disease survey (POSC). The detailed processes of the active components (SSC and POSC) have been described (Grewar et al., 2019a; Grewar & Weyer, 2016) and only information pertinent to this quantitative evaluation of the system as a whole are expanded upon below.

2.3.1 Passive surveillance component (PSC)

Passive surveillance takes place throughout the AHS controlled zone and this component is represented in each surveillance area analysed. The legislative onus on reporting confirmed or suspect AHS cases detected by veterinarians, laboratories or any other person is established in South African law (Animal Diseases Act (Act No.35, 1984)). The PSC in the AHS controlled area of South Africa is explicitly included in South Africa's AHS surveillance strategy. The PSC is primarily reliant on the owners and/or managers of horses detecting suspect cases after clinical signs of the disease are evident, those clinically ill horses being investigated by a veterinarian and samples being taken for AHS diagnosis.

2.3.2 Sentinel surveillance component (SSC)

The sentinel surveillance component refers to the monthly testing of selected sentinels proportionally sampled based on the underlying equine population within the AHS FZ and SZ. This program was initially established specifically to provide the active surveillance basis for AHS freedom for trade with the EU (EC, 2008). While the program does include serological testing of approximately 60 animals per month (previously unvaccinated animals), all animals are also tested using a highly sensitive real-time quantitative PCR (RT-qPCR) (Guthrie et al., 2013) with a monthly target of 150 animals. For consistency with other components and our proposed case definition, only the results from the PCR based sentinel testing were considered for this analysis. Full reports regarding the sentinel program for the

period reviewed in this manuscript are available (Grewar & Weyer, 2018; Grewar, Weyer, Burger, Russouw, & Parker, 2016; Grewar et al., 2017).

Results from the sentinel surveillance program were obtained by permission from the Western Cape Department of Agriculture (WCDOA). Sentinel surveillance is only performed in the FZSZ_CZ and FZSZ_NonCZ. Table 1 shows the surveillance period, sampled totals and associated herd and horse-level census pertaining to the SSC.

Table 1

Sentinel surveillance component – number of sentinel herds and horses tested with underlying census represented by sentinel herds. Counts are split between the two surveillance areas that have sentinel surveillance performed within them

Surveillance period (months starting 1 July 2016)	Surveillance evaluation area					
	FZSZ_CZ			FZSZ_NonCZ		
	Number of sentinel herds	Number of horses in sentinel herds	Number of sentinels tested	Number of sentinel herds	Number of horses in sentinel herds	Number of sentinels tested
1	13	430	37	40	723	133
2	13	430	41	42	735	132
3	13	448	47	37	611	110
4	13	448	46	35	604	108
5	13	448	47	35	598	107
6	12	418	45	37	611	104
7	12	418	43	38	614	105
8	12	418	44	37	611	103
9	12	418	43	36	597	103
10	13	420	47	32	553	97
11	12	418	42	35	573	100
12	12	370	42	28	458	82
13	13	420	44	33	575	95
14	12	410	41	32	532	90
15	12	410	43	34	570	89
16	14	448	47	36	606	101
17	13	430	47	34	596	97
18	13	413	49	33	514	90
19	13	412	50	37	520	97
20	13	412	43	37	596	103
21	14	419	54	38	599	105
22	13	371	46	39	646	106
23	14	419	45	37	594	98
24	15	539	47	38	600	101

FZSZ_CZ: AHS free and surveillance zone within the 2016 AHS outbreak containment zone

FZSZ_NonCZ: AHS free and surveillance zone outside the 2016 AHS outbreak containment zone

2.3.3 Post-outbreak freedom from disease survey component (POSC)

A stand-alone freedom from disease survey targeting the containment zone of the 2016 Paarl outbreak was undertaken in March 2017 (Grewar et al., 2019a). Data from this study

was integrated into the surveillance dataset used in this evaluation. The number of herds and animals within herds differ slightly to the published reference to this component since census data was extracted from the WCDOA in March 2019 for this evaluation, as described below. For this component a total of 262 horses in 51 herds were tested using the same real-time quantitative PCR as in the SSC and represented 2235 horses in total. The POSC is only relevant in the FZSZ_CZ and for one surveillance period, namely March 2017 (i.e. surveillance period nine).

2.4 Population of interest

Herd location and herd-level census data were provided by the WCDOA and were generated from movement permits, historical outbreak censuses, vaccination authorisation and routine censuses undertaken in the controlled area. The population of interest was limited to domestic horses. The AHS controlled area does contain small populations of zebra (555 animals in 54 herds in the SZ and 1068 animals in 81 herds in the PZ) and donkeys (115 animals). These species do not, however, show overt clinical signs of the disease (Coetzer & Guthrie, 2004) and are therefore not represented in passive surveillance activities. Donkeys were not specifically excluded from active surveillance programs but, because of their low population size, were not represented in either the SSC or the POSC.

The census information used in this evaluation was based on a once-off data extraction in March 2019, and that herd-level population was duplicated for each surveillance period. The total herds and associated horses per surveillance area are shown in Table 2 and the locations of these herds are shown in Figure 1.

Table 2

Census information of herds and horses within the African horse sickness (AHS) controlled area of South Africa.

Surveillance area	Number of herds	Number of horses (mean per herd/median per herd)
FZSZ_CZ	234	4476 (19/6)
FZSZ_NonCZ	890	8386 (9/4)
PZ	233	3655 (16/4)
Total	1357	16517 (12/4)

FZSZ_CZ: AHS free and surveillance zone within the 2016 AHS outbreak containment zone

FZSZ_NonCZ: AHS free and surveillance zone outside the 2016 AHS outbreak containment zone

PZ: protection zone

2.5 Surveillance case definition

The case definition for all three surveillance components is based on the OIE's case definition for infection of African horse sickness (OIE, 2016b). Given the lack of pathognomonic clinical signs for the disease, however, the end-point of all components' detection nodes is based on laboratory testing. Although investigations into suspect cases of AHS include diagnostic tests other than the RT-qPCR, the group-specific RT-qPCR is the entry-point into the laboratory testing process. All positive cases would include a positive RT-qPCR test. No cases of AHS were detected or reported during the surveillance period evaluated. Accurate information on numbers of passive surveillance investigations and negative clinical reporting is not available. In the SSC program a total of 8 horses were investigated to a negative conclusion between July 2016 – June 2018 (Grewar & Weyer, 2018; Grewar, Weyer, Burger, Russouw, & Parker, 2016; Grewar et al., 2017). Details of screening tests and investigations of the POSC have been published (Grewar et al., 2019a). We conclude that all suspect cases detected through any of the surveillance programs were followed until AHS infection was ruled out. The specificity of each surveillance component (the probability that a negative disease status will have a negative surveillance outcome) is therefore considered as 100%.

2.6 Scenario tree

A graphical representation of the scenario tree depicting the evaluation of all three surveillance components is shown in Figure 2 with descriptions of nodes and branch distributions/proportions included in Table 3.

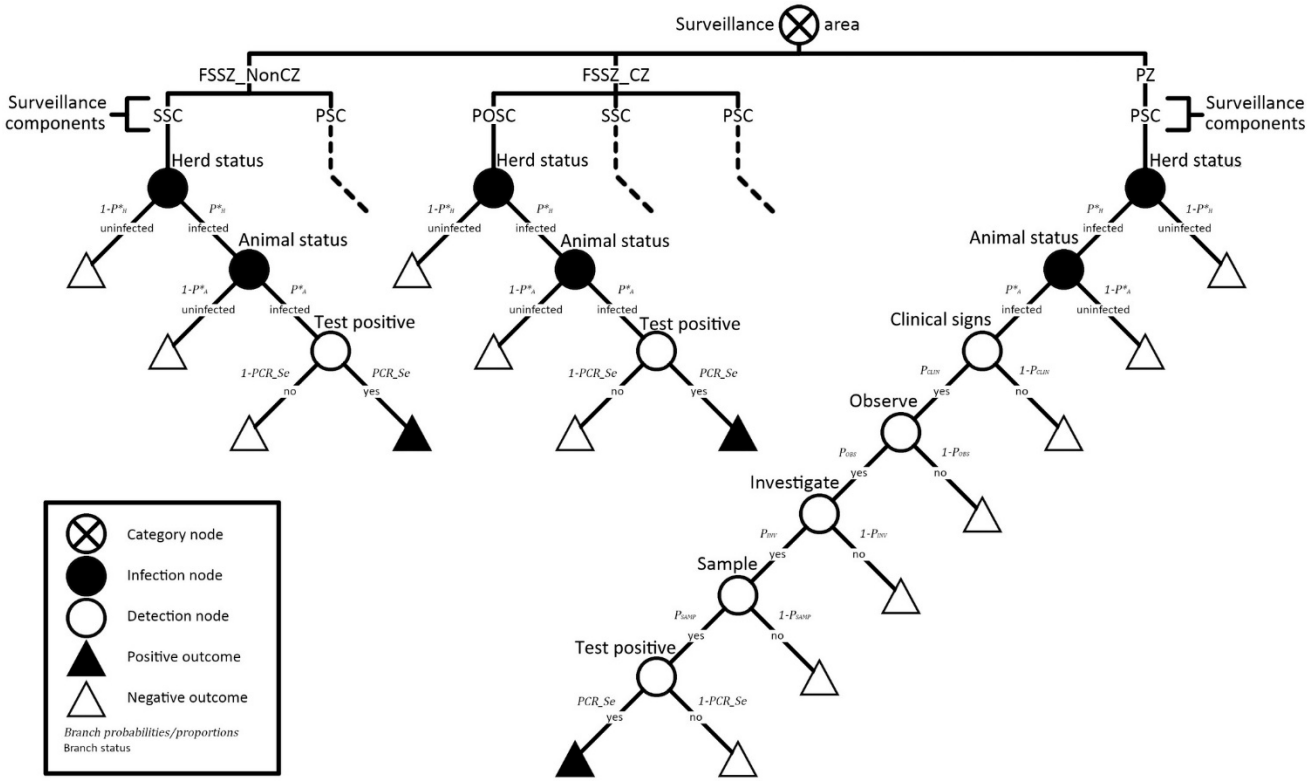

Figure 2

Scenario tree depicting the evaluation of three surveillance components within the African horse sickness (AHS) control area of South Africa. Descriptions, values and distributions of branch probabilities and proportions are described in Table 3. Dashed lines indicate relevant surveillance components within the associated surveillance area but that are identical and shown in another surveillance area. Note that in the PZ only the PSC is relevant and no active surveillance programs take place in this area. PSC: Passive surveillance component; SSC: Sentinel surveillance component; POSC: Post-outbreak stand-alone surveillance component; FZSZ_CZ: AHS free and surveillance zone within the 2016 AHS outbreak containment zone; FZSZ_NonCZ: AHS free and surveillance zone outside the 2016 AHS outbreak containment zone; PZ: protection zone

Table 3

Input parameters for the African horse sickness surveillance evaluation model

Input parameter	Parameter code	Value	Applicable surveillance components	Explanation and source
Animal-level design prevalence	P_A^*	1 animal per herd	All	
Herd-level design prevalence	P_H^*	0.01	All	Estimate based on herd-level prevalence from outbreak data between 1997 and 2016
Probability of freedom from AHS at surveillance period 1	$PriorPfree_1$	0.5	All	Initial probability of freedom in surveillance period 1 (July 2016) reflecting an uninformed prior
Sensitivity of RT-qPCR	PCR_Se	$Beta\,(9.65,1.19)$	All	Sensitivity of the RT-qPCR used for laboratory testing of AHS derived from a median value of 0.978 (95% interval of 0.708 -0.9996) (Guthrie et al., 2013; Sergeant, Grewar, Weyer, & Guthrie, 2016)
Probability of introduction of AHS in each surveillance period	$Pintro$	$Pert\,(0.017, 0.033, 0.067)$	All	Value is based on the number of outbreaks in the AHS controlled area in the 210 months since 1 January 1999. 1999 was the first year since the regionalisation of South Africa in AHS controlled zones that an outbreak occurred. The Pert distribution accounts for variability in $Pintro$ with half and double the actual outbreak incidence as lower and upper bounds as previously described (Alban, Boes, Kreiner, Petersen, & Willeberg, 2008).
Probability of infected animal showing clinical signs	P_{CLIN}	$Beta(c_i + 1, n_i - c_i + 1)$	PSC	Probability of individual infected animal showing clinical signs of AHS based on the clinical case proportions observed in randomly selected outbreak i†. Based on the Bayesian estimate of a population proportion where clinical signs (c) are successes of n cases observed in outbreak i (Vose, 2008)
Probability of horse owner/manager detecting horse showing clinical signs of AHS	P_{OBS}	$Pert\,(i\_lower, i\_most\ likely, i\_upper)$	PSC	Randomly selected expert opinion from expert i on the probability that a herd owner/manager will observe an infected animal showing clinical signs of AHS*
Probability of horse being investigated by a veterinarian	P_{INV}	$Pert\,(i\_lower, i\_most\ likely, i\_upper)$	PSC	Randomly selected expert opinion from expert i on the probability that a herd owner/manager will request a veterinarian to investigate an infected animal observed to have been showing clinical signs of AHS*
Probability of sample being taken for AHS testing	P_{SAMP}	$Pert\,(i\_lower, i\_most\ likely, i\_upper)$	PSC	Randomly selected expert opinion from expert i on the probability of a veterinarian obtaining a sample from a horse whose owner requested an investigation for*

†Only outbreaks where subclinical cases were detected and reported on are included here – namely 2011, 2014 (both outbreaks) and 2016

*Expert opinion is area-based and random selection of an expert for his/her opinion is performed for each calculation based on where the relevant herd is situated. Experts gave a most likely, a lower and an upper estimate for each probability

AHS – African horse sickness

2.6.1 Herd and animal design prevalence

The probability that a herd is infected (P_H^*) was estimated as 1%. This was based on the herd-level prevalence from described AHS outbreaks in the AHS controlled area between 1999 and 2016 assuming an underlying herd population of 1357 herds (Table 2). In this period an average of 18 herds were affected per outbreak (Grewar et al., 2019b; Weyer et al., 2016; WCDOA unpublished outbreak data). For animal-level prevalence (P_A^*): since the herd size throughout the AHS controlled area is relatively small (Table 2), using a percentage based P_A^* was not meaningful, and the animal detection level was set as an integer value of

one infected animal per herd. The design prevalence set for the study was, therefore, one animal in 1% of herds which translates to one infected animal in approximately two infected herds within the FZSZ_CZ and PZ and 9 infected herds within the FZSZ_NonCZ.

2.6.2 Probability of detection

All three surveillance components depended upon the sensitivity of the RT-qPCR (PCR_Se) used routinely for surveillance and investigation in the AHS controlled area. This was modelled as a $Beta(9.65, 1.19)$ distribution as previously defined (Sergeant et al., 2016). For the SSC and POSC, the animal level sensitivity SeU is equivalent to PCR_Se.

For the PSC four detection nodes define the probability that samples from infected horses were presented for testing for AHSV. The first was the probability of clinical signs being exhibited by an infected horse (P_{CLIN}). This probability was modelled as Beta distributions based on the proportion of known infected animals that showed clinical disease observed in the outbreaks in the AHS controlled area where subclinical cases had been detected – namely the 2011, 2014 (two separate outbreaks) and 2016 outbreaks. In those four outbreaks there were 15, 52, 17 and 14 subclinical cases of the 84, 89, 22 and 21 cases in total respectively (Grewar et al., 2019b; Weyer et al., 2016). The four Beta distributions were based on the Bayesian estimate of a population proportion (Vose, 2008) where cases showing clinical signs (c) are successes of n outbreak cases. A random selection from any of the four distributions was made to inform P_{CLIN} for each iteration of the model.

Expert opinion was elicited to establish the likelihood that these infected horses, that are showing clinical signs, will be detected by owners/managers (P_{OBS}), investigated by a

veterinarian (P_{INV}) and sampled for testing for AHS infection (P_{SAMP}). Experts were selected based on the primary investigator's knowledge of equine veterinarians working the AHS controlled area and included both private practitioners (n=9) and regulatory veterinarians (n=3) with experience in the equine field. Opinions were obtained through structured telephonic interviews where responses were independent of other experts. Each expert gave opinion relative to the surveillance area/s in which they confirmed they had a reliable opinion, and each opinion included the expert's minimum, most likely and maximum estimate of the probability described. Expert opinion probabilities were not aggregated but rather an individual opinion was randomly selected, with replacement, for each model iteration from the pool of opinions relative to the underlying surveillance area. The selected opinion was converted into a Pert distribution with the expert's minimum, most likely and maximum correlating to the same values within the Pert distribution, and a random value from this distribution was extracted per iteration. Supplementary table 1 gives the raw expert opinion data obtained while Table 4 gives the summarised outcome. The animal-level sensitivity (SeU) for the PSC was calculated as the product of P_{CLIN}, P_{OBS}, P_{INV}, P_{SAMP} and PCR_Se.

Table 4

Expert opinion summary of the probabilities of the observation of clinically ill horses, the investigation of these horses and the probability of sampling with the goal of testing for African horse sickness. The median and range of probabilities given are shown for the minimum estimate, the most likely estimate and the maximum estimate given by experts. The estimates are categorised by the applicable surveillance area under evaluation.

Surveillance evaluation area	Number of expert opinions elicited	Model parameter	Median and range of probabilities obtained		
			Minimum estimate	Most likely estimate	Maximum estimate
FZSZ_CZ	4	P_{OBS}	0.625 (0.5-0.8)	0.8 (0.8-0.94)	0.93 (0.9-1.0)
		P_{INV}	0.65 (0.5-0.9)	0.8 (0.7-0.98)	0.95 (0.8-1.0)
		P_{SAMP}	0.825 (0.7-0.9)	0.95 (0.8-0.95)	1.0 (0.9-1.0)
FZSZ_NonCZ	6	P_{OBS}	0.5 (0.4-0.8)	0.725 (0.48-0.95)	0.945 (0.75-1.0)
		P_{INV}	0.6 (0.4-0.8)	0.7 (0.6-0.9)	0.8 (0.8-1.0)
		P_{SAMP}	0.825 (0.55-0.9)	0.95(0.6-0.95)	1.0 (0.9-1.0)
B : PZ	7	P_{OBS}	0.7 (0.1-0.8)	0.8 (0.7-0.94)	0.96 (0.8-1.0)
		P_{INV}	0.6 (0.1-0.9)	0.8 (0.65-0.95)	1.0 (0.85-1)
		P_{SAMP}	0.9 (0.5-1.0)	0.95 (0.6-1.0)	1.0 (1.0-1.0)
All areas	17	P_{OBS}	0.6 (0.1-0.8)	0.8 (0.48-0.95)	0.96 (0.75-1.0)
		P_{INV}	0.6 (0.1-0.9)	0.7 (0.6-0.98)	0.95 (0.8-1.0)
		P_{SAMP}	0.85 (0.5-1.0)	0.95 (0.6-1.0)	1.0 (0.9-1.0)

FZSZ_CZ: AHS free and surveillance zone within the 2016 AHS outbreak containment zone

FZSZ_NonCZ: AHS free and surveillance zone outside the 2016 AHS outbreak containment zone

PZ: protection zone

2.7 Probability of introduction

For calculations where the probability of freedom of a surveillance period was determined a probability of introduction ($Pintro$) was required. This value was estimated from the historical number of new disease incursions (n=7) detected in the AHS controlled area between 1 January 1999 and the start of the surveillance evaluation, a total of 210 months. Though the probability of introduction calculated in this manner would decrease during the evaluation, to remain conservative the value at the first surveillance period was used throughout. To establish a realistic input distribution for $Pintro$, the periods at risk were both halved and doubled to establish the upper and lower limits of a Pert distribution, $Pert(0.017,0.033,0.067)$, from which a random value per iteration was extracted (Alban et al., 2008).

2.8 Unadjusted herd sensitivity, component sensitivity and component probability of freedom

Herd-level sensitivity was estimated based on the equation adapted from (MacDiarmid, 1988) for each surveillance period evaluated using the hypergeometric approximation so that the herd sensitivity for each herd h is:

$$SeH_h = 1 - (1 - SeU \times \frac{n}{N})^d \quad (1)$$

where n is the number of horses screened, N the total number of animals in the herd and d the integer number of infected animals per herd. For herd-level sensitivity d equated to 1.

The unadjusted surveillance component sensitivity is determined through the same equation as the herd sensitivity (Eq. 1) except that, since the sensitivity for each herd varies, SeU is the mean of SeH across all herds and herd level values are used for n, N and d. For herd-level calculations $d = P_H^* \times N$ rounded up to the next integer and P_H^* is the herd-level design prevalence. As for herd-sensitivity calculations for the PSC, all herds are subject to surveillance so that $n = N$.

The unadjusted probability of freedom for each surveillance component for each surveillance period t was established to estimate the freedom probability each component would result in independent from other components. The probability of freedom for each surveillance period is dependent on the component sensitivity (CSe) and the posterior probability of freedom for the preceding period ($PriorP_{free}$) so that

$$P_{free} = \frac{PriorP_{free}}{1 - CSe_t \times (1 - PriorP_{free})} \quad (2)$$

The prior probability of freedom is revised for each surveillance period to account for the probability of infection exceeding the design prevalence during the surveillance period, through either an increase above the threshold of an undetected existing infection or the introduction of a new infection (P_{intro}) so that

$$PriorP_{free_t} = 1 - [1 - Pfree_{t-1} + P_{intro_t} - \left((1 - Pfree_{t-1}) \times P_{intro_t}\right)] \quad (3)$$

For the first surveillance period, an uninformed prior probability of freedom of 0.5 was used.

2.9 Adjusted overall system sensitivity and overall probability of freedom

In establishing the overall system sensitivity and probability of freedom we did not assume independence between surveillance components since herds involved in either of the active surveillance programs (SSC and POSC) would be included in the PSC (Martin et al., 2007, para. 5.2). In short: for each surveillance period, we estimated herd-sensitivity (Eq. 1) and the resulting posterior probability of infection ($PostPInf$) for all herds in the PSC, where $PostPInf_h = 1 - Pfree_h$. $Pfree_h$ is calculated using Eq. 2, substituting SeH_h for CSe and $1 - P_H^*$ for $PriorP_{free}$. This process was repeated successively for the SSC and POSC.

The component sensitivity for the PSC (CSe_{PSC}) was then estimated in the same manner as previously, assuming independence, while adjusted component sensitivities for the SSC and POSC were estimated substituting mean values of $PostPInf$ for the PSC and SSC, respectively, as shown in Eq. 4.

$$CSe_{SSC,POSC} = 1 - (1 - mean(SeH_h) \times \frac{n}{N})^{mean(PostPInf_h) \times N} \quad (4)$$

The final system sensitivity per surveillance period per surveillance area is calculated by

$$SSe_{adjusted} = 1 - \Pi\ (1 - CSe_i) \quad (5)$$

The system probability of freedom is derived from the system sensitivity similarly to each component (Eq. 2) except the adjusted SSe is used instead of CSe. The prior probability of freedom for each period is revised for each time step as in Eq. 3.

2.10 Sensitivity analysis

To establish which inputs (P_{CLIN}, P_{OBS}, P_{INV}, P_{SAMP} and PCR_Se) had the largest impact on the system sensitivity (SSe), Spearman's correlation coefficients were derived for each combination. Coefficients were depicted in tornado plots (Supplementary figure 1). To evaluate the impact of P_{intro} on the final probability of freedom we estimated the maximum probability of freedom ($Pfree_{equilibrium}$: equilibrium probability of freedom) from mean P_{intro} and system sensitivity (Watkins, Martin, Kelly, Madin, & Watson, 2009) as

$$Pfree_{equilibrium} = (1 - \frac{P_{intro}}{SSe})/(1 - P_{intro}) \quad (6)$$

where values for P_{intro} and SSe were mean values of the final surveillance period. Permutations of $PFree_{equilibrium}$ were established for changing P_{intro} values from the simulated mean and for 5% increments between 5-25%.

3. Results

3.1 Probability of freedom

The final probability of freedom for each surveillance area is shown in Table 5 and is categorised by the overall system and independent component probability of freedom. Figures 3 to 5 show the graphical representation of the changing probability of freedom for both the system and independent components where applicable. Note that the PSC is the

only component implemented in the PZ surveillance area; hence the system and component outcomes are equivalent. A median probability of between 98.3 and 99.8% was the final posterior probability of freedom across the controlled area after 24 months. This level had been obtained by the 9th, 3rd and 7th period in the FZSZ_CZ, FZSZ_NonCZ and PZ respectively. In general, a plateau of median freedom probability had been obtained throughout by approximately 4 months into the surveillance. The uncertainty surrounding the median system probability of freedom, as shown in the 95% PI band in Figures 3 to 5, reached stable levels at approximately the same period as when the final probability of freedom had been achieved.

Table 5

Final adjusted system and unadjusted component posterior probability of freedom after 24 months of surveillance after the Paarl 2016 outbreak in the African horse sickness (AHS) controlled area of South Africa

Surveillance evaluation area	Overall system		PSC		SSC		POSC*	
	Median	95% PI	Median	95% PI	Median	95% PI	Median	95% PI
FZSZ_CZ	0.983	0.911-0.999	0.982	0.904-0.999	0.271	0.171-0.381	0.227	0.14-0.325
FZSZ_NonCZ	0.998	0.975-1	0.998	0.972-1	0.575	0.406-0.716	NA	
PZ	0.984	0.906-1	0.984	0.906-1	NA		NA	

* The POSC took place in period 9 alone although the value reflects the 24th month posterior probability of freedom

PSC: Passive surveillance component

SSC: Sentinel surveillance component

POSC: Post-outbreak stand-alone surveillance component

PI: Probability interval

FZSZ_CZ: AHS free and surveillance zone within 2016 AHS outbreak containment zone

FZSZ_NonCZ: AHS free and surveillance zone outside of 2016 AHS outbreak containment zone

PZ: protection zone

NA: Not applicable

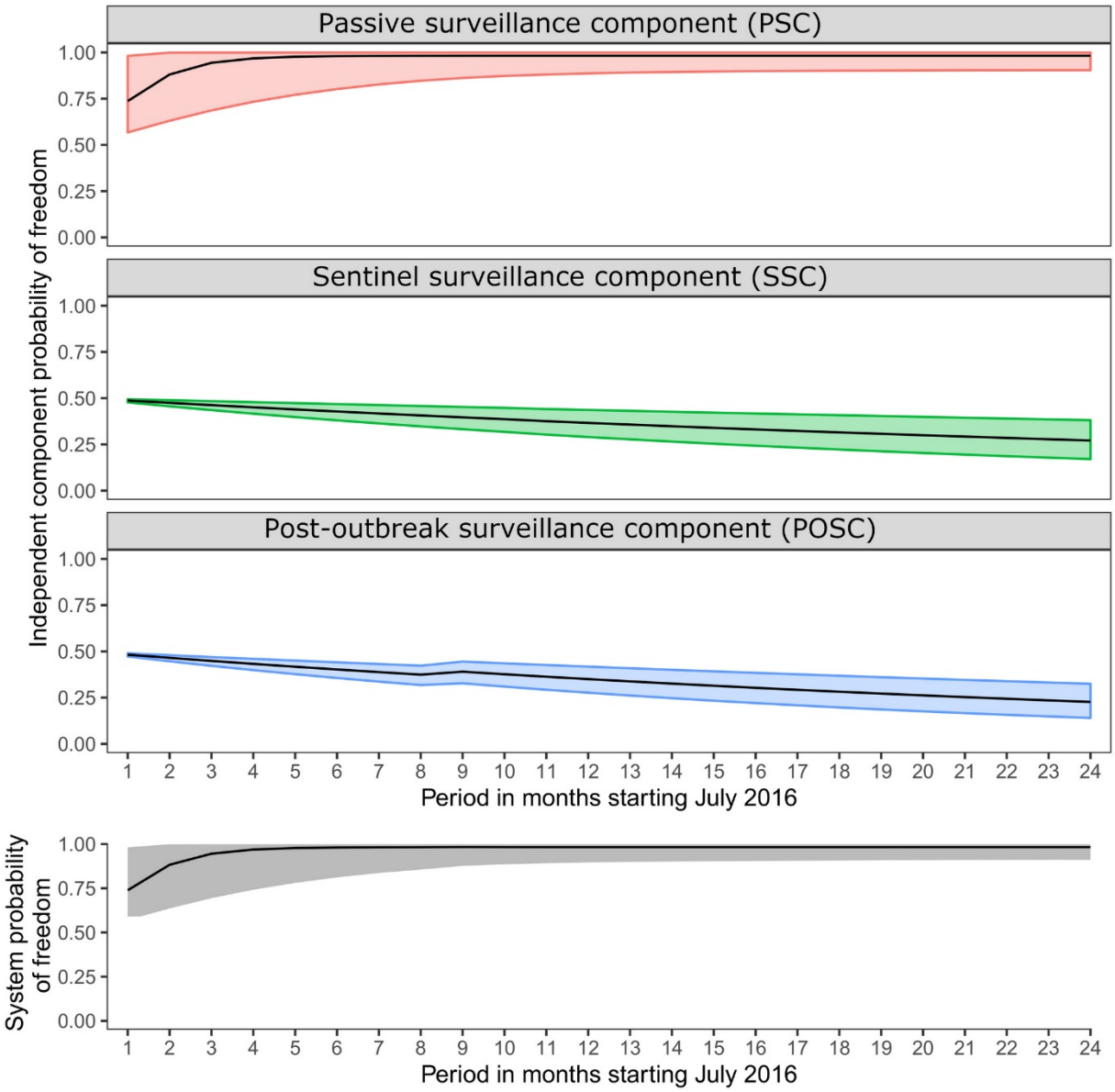

Figure 3

Overall system and independent component probability of freedom from African horse sickness in the free and surveillance zone within the 2016 AHS outbreak containment zone (FZSZ_CZ) by monthly periods over 24 months starting July 2016. The black line per plot indicates the median probability of freedom with shaded bands indicating the 95% probability interval.

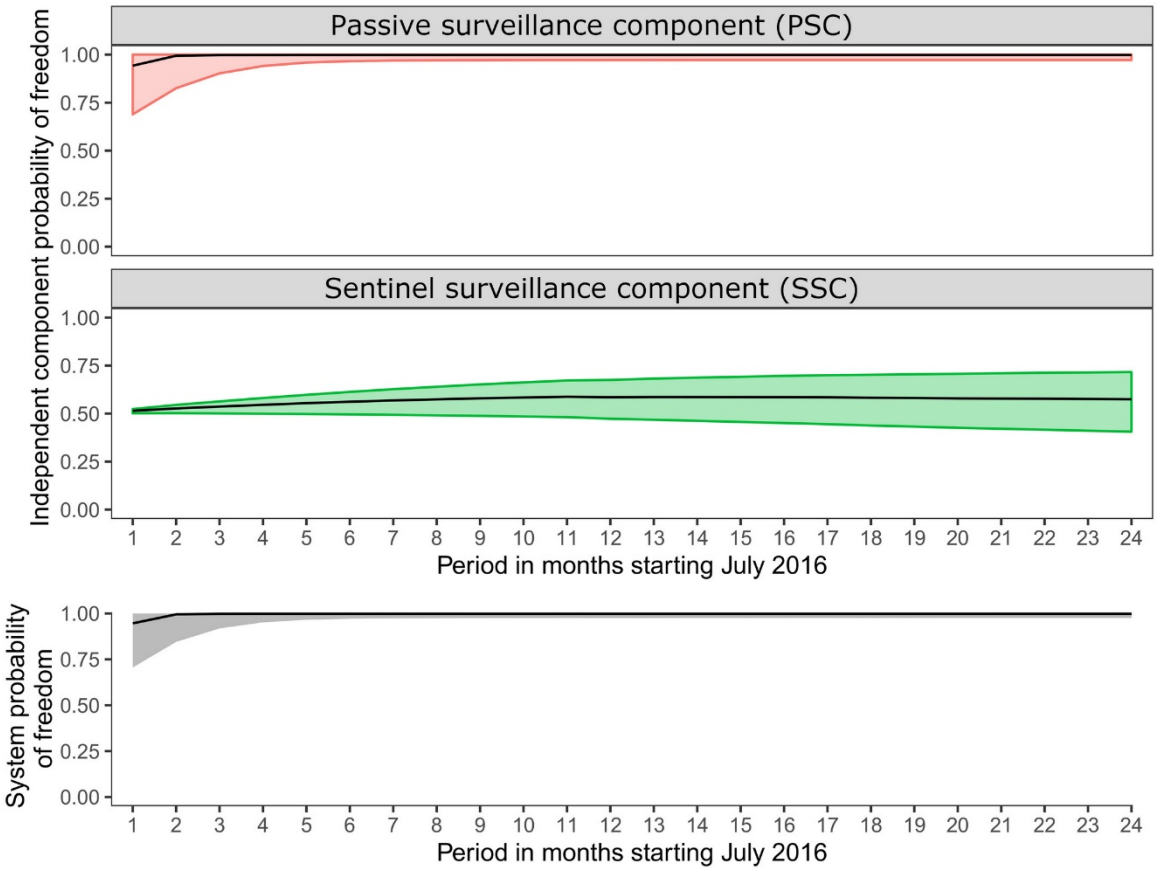

Figure 4

Overall system and independent component probability of freedom from African horse sickness (AHS) in the free and surveillance zone outside the 2016 AHS outbreak containment zone (FZSZ_NonCZ) by monthly periods over 24 months starting July 2016. The black line per plot indicates the median probability of freedom with shaded bands indicating the 95% probability interval.

The high levels of freedom probability attained by the PSC are reflected in the system outcome, and this component is the driver of the overall system probability of freedom. The SSC independently did not provide a probability of freedom much above the prior probability of freedom of 50% for the FZSZ_NonCZ, and for the FZSZ_CZ this component failed to increase with regards to probability of freedom over time.

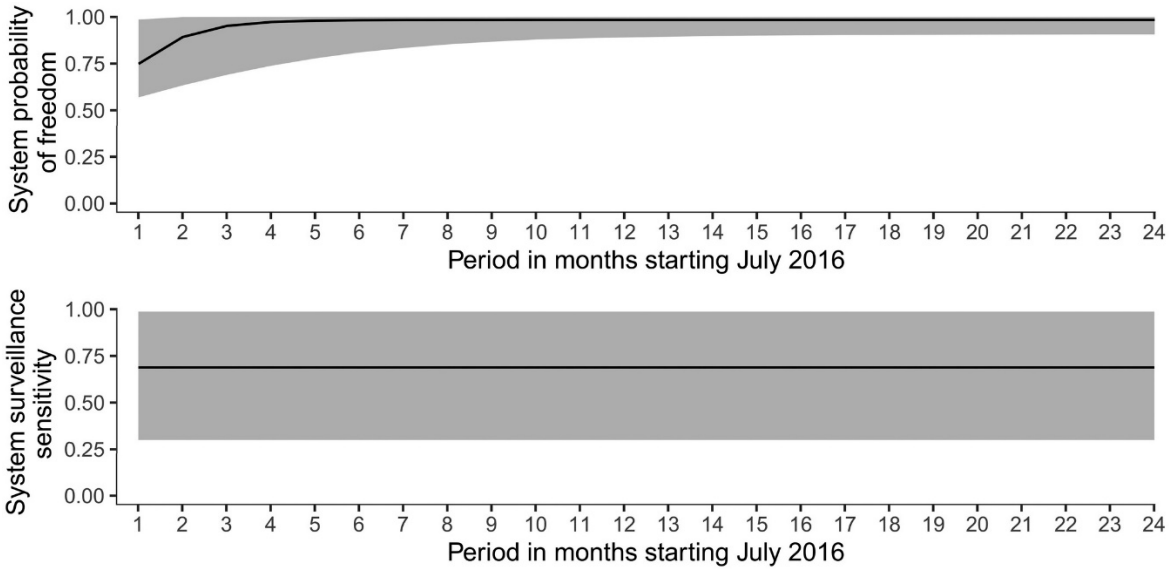

Figure 5

Overall system sensitivity and probability of freedom from African horse sickness in the protection zone (PZ) by monthly periods over 24 months starting July 2016. The black line per plot indicates the median sensitivity and probability of freedom with shaded bands indicating the 95% probability interval.

3.2 Surveillance sensitivity

The sensitivity of surveillance for the PSC remains constant in each surveillance period for both the system and independent components, since the evaluation used a fixed herd-level population throughout. The PSC had consistently higher median surveillance sensitivities when compared to active components in the same area (Figures 6 and 7) and this drives the relatively stable system sensitivities throughout. While the median sensitivity of the SSC was higher for the FZSZ_NonCZ compared to the FZSZ_CZ, the sensitivity of this component, in general, had low sensitivity at levels below 15%. The only perceptible difference that the POSC had on the results was a slight improvement in the 2.5% lower probability level of the system sensitivity of surveillance in the month the survey was performed (Figure 6 period 9).

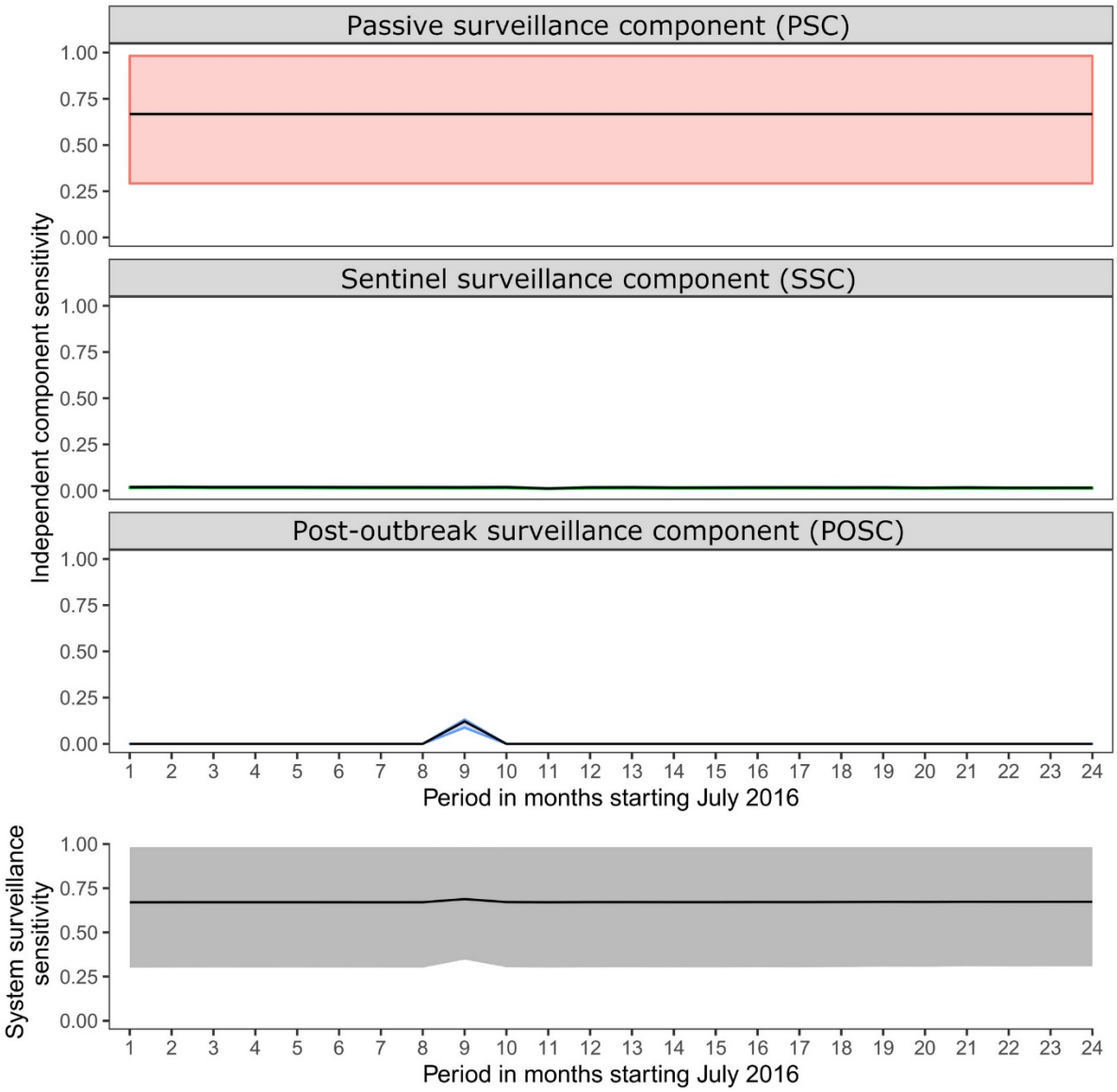

Figure 6

Overall system and independent component sensitivity of surveillance in the AHS free and surveillance zone within the 2016 AHS outbreak containment zone (FZSZ_CZ) by monthly periods over 24 months starting July 2016. The black line per plot indicates the median sensitivity with shaded bands indicating the 95% probability interval.

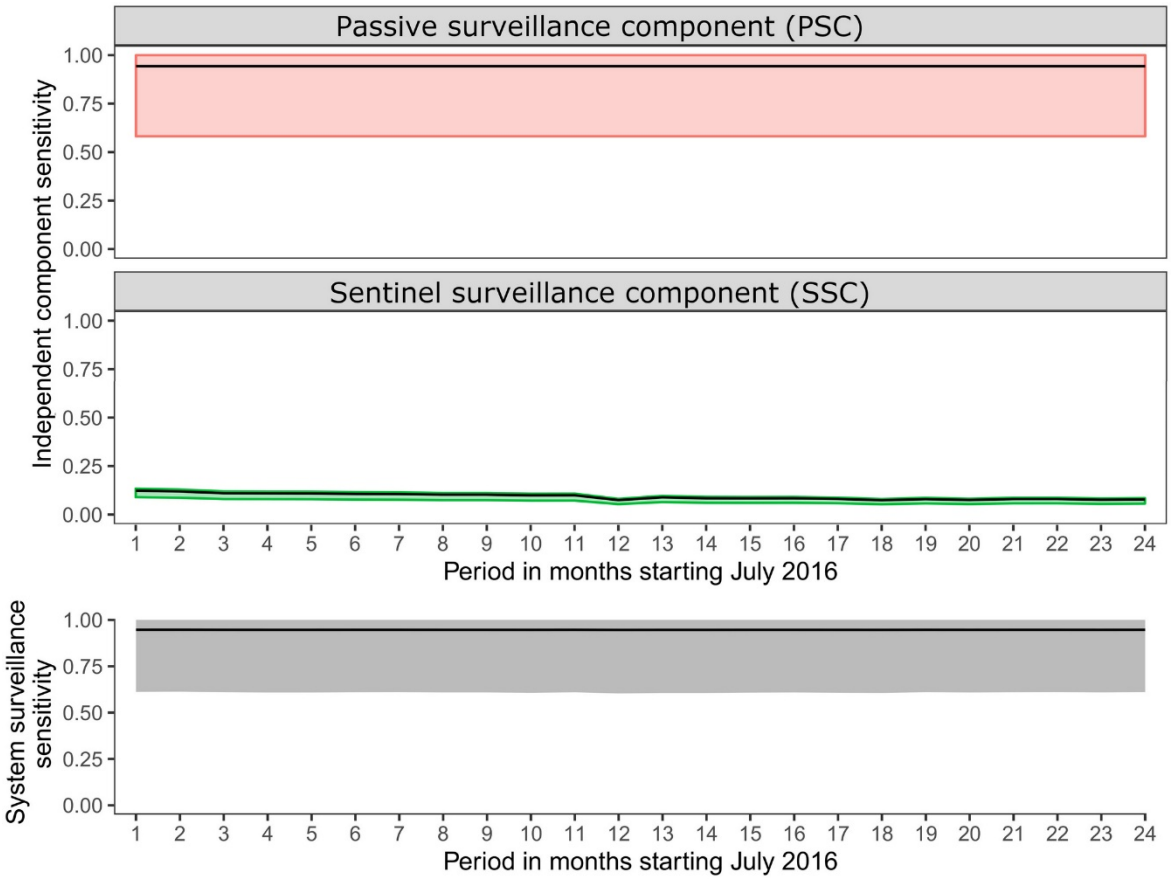

Figure 7

Overall system and independent component sensitivity of surveillance in the AHS free and surveillance zone outside the 2016 AHS outbreak containment zone (FZSZ_NonCZ) by monthly periods over 24 months starting July 2016. The black line per plot indicates the median sensitivity with shaded bands indicating the 95% probability interval.

3.3 Sensitivity analysis

Tornado plots of the Spearman's correlation coefficients are depicted in Supplementary figure 1. The probability that horses showed clinical signs was the factor that influenced system sensitivity most with coefficients of 0.904, 0.928 and 0.935 for the FZSZ_NonCZ, FZSZ_CZ and PZ respectively. The expected maximum probability of freedom is depicted in Table 6 for each surveillance area and with varying inputs of P_{intro}.

Table 6

Expected maximum probability of freedom (*PFreeEquil*) based on the simulated mean probability of introduction (*Pintro*) and system sensitivity (*SSe*) as well as for changing values of probability of introduction between 5% and 25%

Surveillance evaluation area	Actual simulation values			Evaluation of changing *Pintro* values				
	mean *SSe*	Mean *Pintro*	*PFreeEquil*	5%	10%	15%	20%	25%
FZSZ_CZ	0.679	0.036	0.982	0.975	0.947	0.917	0.882	0.842
FZSZ_NonCZ	0.909	0.036	0.996	0.995	0.989	0.982	0.975	0.967
PZ	0.691	0.036	0.983	0.976	0.950	0.921	0.888	0.851

FZSZ_CZ: AHS free and surveillance zone within the 2016 AHS outbreak containment zone

FZSZ_NonCZ: AHS free and surveillance zone outside the 2016 AHS outbreak containment zone

PZ: protection zone

4. Discussion

4.1 Probability of freedom and surveillance sensitivity

Our model provides simulated results for specific surveillance areas which were defined by different combinations of surveillance components. The estimates show high (>98%) posterior probabilities of freedom throughout the AHS controlled area in the 24 months succeeding an AHS outbreak. The passive surveillance component drives the high estimates of the system probability of freedom. The practicality of this has been shown through the historical detection of outbreaks in the AHS controlled area where all outbreaks, since 1997, have been detected through passive surveillance. The primary reason passive surveillance has such a high comparative impact on final system outcomes is that every horse and every herd contribute to this component which drives up the herd, component and finally system sensitivity, and hence probability of freedom. The probabilities within the passive component which may decrease its effectiveness are those that influence whether infected horses show clinical signs and whether clinically suspect affected horses are identified, investigated and tested for AHS. Clinical signs of AHS can include fever, pulmonary distress, subcutaneous oedema (primarily of the head and neck) and death in severe cases. Signs are,

however, generally not pathognomonic (Coetzer & Guthrie, 2004), but the clinical nature of AHS does make it a disease that is conducive to passive surveillance. The passive surveillance detection node probabilities associated with the observation, investigation and sampling of suspect cases, based on expert opinion, were generally high (median most likely estimates between 70%-95%). This illustrates the advantage of having a well-defined legislated disease control area and where a high level of contact occurs between veterinarians, the public and regulatory officials as a result of regulations surrounding AHS vaccination and movement control. The higher estimates of the model in the FZSZ_NonCZ occur as a result of the higher number of horses and herds in this area compared to the other surveillance areas considered.

The active surveillance components generally had low sensitivity and final probability of freedom outcomes. For instance, by the time the POSC survey was performed in period nine in the FZSZ_CZ the median and 95% probability interval of probability of freedom in that area were almost at stable levels similar to the final posterior probabilities of freedom after 24 months. It should be noted that the active components were not designed at the design prevalence evaluated here and both were designed assuming a single homogenous population (single-stage design). Theoretically one could remove the active components from the surveillance programs for the AHS controlled area with negligible effect on overall sensitivity and probability of freedom. The resources required for active surveillance are substantial – the POSC cost approximately 15 500 USD (R210 000) while the sentinel surveillance program costs approximately 105 000 USD (R1.476 Million) per year (Grewar et al., 2017, 2019). If these resources were spent on further improving passive surveillance, and in particular the probability of clinically suspect horses being presented for AHS testing,

the surveillance program would be simplified without losing sensitivity. In general, improvements along the passive surveillance scenario pathway would be best achieved through improved communication and education of horse owners, veterinarians and laboratories involved in AHSV testing, with ensuring capacity for testing in the latter also an important consideration. The practical consequences of utilising a passive surveillance program alone would, however, need to be carefully considered and further studied. It is likely that, by simply performing active surveillance, the sensitivity of the passive surveillance program is improved by raising awareness through dissemination of disease and surveillance information and results to stakeholders.

It is likely that impoverished communities have limited access to affordable veterinary care, and this is likely to decrease the effectiveness of passive surveillance. Two horse sub-populations in communities in the AHS controlled area where this may be evident have been associated with AHS outbreaks in the recent past – Mamre in 2011 (Grewar et al., 2013) and Saron in 2014 (Weyer et al., 2016). In these communities, the Government veterinary service plays an integral role in passive surveillance, through the work of animal health technicians, in order to avoid non-reporting of clinical signs associated with AHS. While the use of probability distributions for the expert opinion detection nodes in the scenario tree accounts for uncertainty of these surveillance events, further investigation of sub-populations of both equines and their owners would provide additional certainty to the evaluation of the passive surveillance component. If specific sub-populations were present these could be included as separate risk categories in the analysis.

The decision to evaluate AHS surveillance for two years was not arbitrary. This period is applicable in both EU and OIE legislation relating to the period of trade suspension or AHS freedom status in the post-outbreak period respectively (EC, 2010 Article 2(f); OIE, 2016b, 2018). Our results show that, at least for the probability of freedom based on surveillance, the 24-month posterior probability of freedom is attained well within 12 months during the post-outbreak period. The seasonality of outbreaks does have relevance, however. Outbreaks in the controlled area of South Africa have occurred in late summer and early autumn. This implies that the first few months of the post-outbreak period occurs in winter where the likelihood of transmission of AHSV is decreased due to the impact cold weather has on both vector proliferation, biting rates and virus replication within the vector (Backer & Nodelijk, 2011; Meiswinkel, Venter, & Nevill, 2004). This results in a natural control mechanism that provides additional confidence in initial probability of freedom estimates.

The sensitivity analysis showed that the probability that a horse shows clinical signs of infection is an important component of the model. The observed variability in P_{CLIN} is due to the variability in the clinical expression of disease in the outbreaks used to model this parameter (which varied considerably). This variability is likely due to the fact that these outbreaks (2011, 2014 (n=2) and 2016) were due to reversion to virulence and/or reassortment of live attenuated vaccine strains (Grewar et al., 2019b; Weyer et al., 2016), with variable virulence, depending on the nature of the reversion and/or reassortment. We would expect outbreaks due to wild strains of virus would generally have high values for P_{CLIN}, and therefore should be more easily detected. Subclinical infection does not imply that no clinical signs are present but rather that they are below the threshold of normal detection. Public education of the clinical presentation of AHS would lower this threshold.

Increasing the probability of introduction of AHS into the different zones only had a substantial effect in the FZSZ_CZ and PZ where the average surveillance sensitivity was 68 and 69% respectively. Still, however, in these areas, an increase in the probability of AHS introduction to 20% and above (from the simulation mean of 3.6%) was required to bring the maximum probability of freedom down to below 90%.

4.2 Model considerations

This evaluation considers the domestic horse population in the AHS controlled area and does not include donkeys or wild equids such as zebra. Zebra do exist in the AHS surveillance and protection zone and constitute 8.9% of the known equid population in the controlled area. Donkeys, while not explicitly excluded from active surveillance, make up a known total of 0.7% of the equid population. In our opinion, the exclusion of these species does not make a substantial difference to the evaluation. We further believe the domestic horse population is representative enough act as a proxy for any outbreaks occurring in other species where spill-over to the domestic horse population is likely to occur given the vector-borne nature of transmission. Recently it has been shown that the plains zebra (*Equus burchelli*) populations in the Western Cape Province, and in particular within the AHS controlled area, are unlikely to be large enough to allow persistent AHS infection (Porphyre & Grewar, 2019). Surveillance data from these populations would, however, be beneficial to provide a more complete surveillance picture. An analysis of proximity of zebra and/or donkeys to domestic horses would provide further insight into the validity of our assumptions.

The extraction of the underlying population at risk at a single point in time is unlikely to have much impact on overall results. Changes in herd sizes will have no impact on passive surveillance components and only a minor impact on the sentinel surveillance component given that the underlying animal detection prevalence was one infected animal per herd. Changes in the number of herds is also likely to only have a minor impact on any of the components. Based on our personal experience, the demographics of the equine population in the AHS controlled area, both spatially and in terms of numbers of individuals and herds, is unlikely to have changed substantially prior to and during the period analysed.

The choice of the surveillance unit in this study was the individual horse. In research using a similar process, the passive surveillance component is often evaluated at a herd level. Horses are generally not considered a production animal and, even where they are kept for production purposes, such as in the breeding industry, each horse is generally individually identified and their care is very individually intensive. Furthermore, for the active surveillance components, individual horses are considered the surveillance unit and expert opinion that was obtained for the associated detection nodes of the PSC was elicited on an individual horse basis. Evaluating surveillance at individual animal level assumes independence between horses in the same herd and probabilities do not change where multiple cases occur. Our approach is a conservative one due to the choice of a single horse as the within-herd design prevalence, rendering issues of lack of independence of horses within herds irrelevant.

Both the active surveillance components have a degree of selection bias. The SSC animals are selected based on their prior vaccination status since sentinels are not recruited if they

are vaccinated against AHS within the preceding two years. The POSC sampling frame was reliant on the census taken during the 2016 outbreak (Grewar et al., 2019a). We do not believe that this selection bias has a substantial influence on the component analysis and since the PSC was the main driver of system outcomes this is not considered an important issue.

Scenario-tree analysis of surveillance activity forms just a part of surveillance evaluation. While the outputs presented provide a quantitative estimate of the surveillance sensitivity and probability of freedom over a period of time, there are other factors which influence the ability of surveillance to detect disease. Well-described frameworks for the evaluation of surveillance activities in animal health have been published (Calba et al., 2013; Cameron et al., 2014; Comin et al., 2019; Drewe et al., 2015; Hoinville et al., 2013; Muellner et al., 2018); the results of this study would be best contextualised within one of these frameworks to provide a more holistic evaluation of AHS surveillance in the controlled area of South Africa.

5. Conclusion

Given that AHS was not detected by this surveillance system, the probability of being free from AHS after the 24-month post-outbreak period was between 98.3% - 99.8% assuming that, if it were present, it would have a prevalence of at least one infected animal in 1% of herds. The final median probability of freedom had been realised by the 9th month after the 2016 outbreak had been resolved, with a plateau in the probability of freedom obtained by approximately the 4th month across the region. The high level of probability of freedom was driven primarily by the passive surveillance component.

A two-year post-AHS outbreak period is the global standard for the lifting of trade suspension (EU) or regaining AHS freedom (OIE) for affected zones or countries. Our work shows that if surveillance is undertaken in a manner that provides realistic estimates of freedom, the two year period should be reviewed. We would recommend that a re-evaluation of freedom from AHS should be permissible from 6 months after an outbreak has been resolved. Additional confidence in freedom can be provided if a period of low vector abundance has elapsed in the interim.

We have shown that the relative benefit of active surveillance components is minimal if passive surveillance is undertaken in a focussed and measurable manner. We further conclude that, while active surveillance will remain a feature of AHS surveillance and control, resource allocation to activities supporting and developing passive surveillance for the disease would be justified. This would be even more applicable in countries or zones where vaccination is either not permitted or is used in limited areas during outbreaks so that clinical expression of an outbreak is not masked by high herd immunity.

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7. Conflict of Interest

South African Equine Health and Protocols NPC is a registered non-profit company in South Africa (registration number 2017/528099/08). It is privately funded and the funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

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