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1 **Title:** Freedom from Infection: Confirming Interruption of Malaria Transmission

2

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10

11 **Keywords:** Elimination, active surveillance, passive surveillance, negative

12 reporting.

13

14 **Abstract**

15 The global reductions in disease burden and the continued spread of drug and

16 insecticide resistance make malaria elimination both viable and imperative,

17 although this may be more easily achieved in some settings compared to others.

18 Whilst the focus has been on optimal approaches to achieve elimination, less

19 attention has been paid to how to measure the absence of malaria. Measuring the

20 absence of transmission poses a specific challenge in that it involves proving a

21 negative. The concept of freedom from infection, routinely used in veterinary

22 epidemiology, can provide quantitative and reproducible estimates that if

23 infections were present above a predefined (low) threshold, they would be

24 detected with a known uncertainty. Additionally, these methods are adaptable

25 for both passively and actively collected data as well as combining information

26 when multiple surveillance streams are available. Here we discuss the potential
27 application of this approach to malaria.

28 **Measuring Elimination**

29 Good disease surveillance is the foundation for effective public health planning. A
30 successful system should generate timely and actionable information to
31 implement or scale back programs. [1, 2] There is currently a renewed drive to
32 achieve malaria elimination. [3-5] As countries reorient their systems to report
33 the absence of transmission, guidance is needed on how to generate
34 reproducible and evidence-based information for decision-making. [6-8]

35

36 Measuring elimination or the absence of disease/infection/transmission poses a
37 specific challenge in that it involves proving a negative. [9, 10] Proving that
38 infection is present in a population is relatively straightforward, as a single
39 positive case would falsify the hypothesis that no infection is present.

40 Conversely, measuring the absence of infection with routine statistical methods
41 is impractical unless the complete population is sampled with a perfect
42 diagnostic tool. [11, 12] Veterinary epidemiologists routinely face the challenge
43 of 'proving zero' to avoid importation of diseased animals as part of the global
44 trade in livestock. [13] The freedom from infection (FFI) methodology was
45 developed to quantify the probability that disease would be detected if it exists
46 in populations (e.g. farms, herds or flocks) of interest. [14] These established
47 methods provide a set of tools for measuring the probability of having achieved
48 elimination whose concepts are highly applicable and should be explored for use
49 in malaria and other human disease systems.

50

51 In this paper, we introduce the concept of FFI and provide examples of how these
52 tools could be applied to the context of malaria elimination. We focus on
53 passively collected surveillance data (PCD), as this is currently the basis for
54 certification of malaria elimination. [15, 16] However, in recognition of some of
55 the frailties of the health systems that collect and report these data and that
56 multiple sources of data will become increasingly common, we also discuss how
57 passively collected data can be supplemented with active surveillance and how
58 information can be combined to generate realistic estimates of the probability of
59 having achieved FFI.

60

61 **Measuring Zero - Freedom from Infection**

62 Statistical methods for estimating FFI are well established in veterinary
63 epidemiology. [14, 17-19] Briefly, the tools estimate the probability that a
64 surveillance system will detect at least one infected individual if the number of
65 infections is above a pre-determined threshold, or design prevalence (DP - see
66 glossary for key terminology and definitions). This calculation can then be
67 extended to estimate the confidence of freedom from the infection of interest (at
68 the DP) given accumulated negative surveillance according to Bayesian
69 probability theory. This is equivalent to the negative predictive value of the
70 surveillance system. [14] Evidence is accumulated over time to calculate the
71 probability of FFI at the pre-determined time-step, whereby the probability that
72 the area, or flock of interest, is free from infection at the set DP increases with
73 each negative result. [20] If the DP is set at a level below which transmission is
74 unlikely to be sustained, and the probability of FFI remains sufficiently high over
75 a period of time, accounting for the risk of disease re-introduction, then one can

76 state with a level of confidence that the disease of interest has been eliminated.

77 For a more detailed overview of the FFI methodology, readers are referred to

78 supplementary file 1 and the standard text in veterinary epidemiology. [14]

79

80 **Freedom Tools in Practice**

81 To our knowledge, the freedom tools have only been fully applied to human

82 health in one instance. Using historical surveillance data, Watkins et al.

83 calculated the sensitivity of the surveillance system to detect wild poliovirus in

84 Australia and calculated the corresponding estimate of FFI. [21] A similar

85 approach to design elimination programs has been employed for other human

86 diseases. For example, the transmission assessment surveys used in the

87 lymphatic filariasis elimination campaigns used a probabilistic mathematical

88 modeling approach to determine the levels of disease prevalence whereby below

89 this threshold, disease is most likely to die out, leading to elimination. [22, 23]

90 However, there has yet to be any evidence that this approach will lead to disease

91 elimination in the field or if it can be transferred to other disease systems. With

92 elimination of malaria and other infectious diseases a global priority, the

93 available and highly relevant FFI framework should be explored.

94

95 The following examples are generating using the RSurveillance package for R (v

96 3.2.3) with the assumptions and parameters used outlined in box 1 (R code

97 available upon request). All parameters can and should be changed to reflect the

98 specific epidemiological setting in the region of interest.

99

100 *Passive Case Detection*

101 The freedom tools are able to provide actionable information using routinely
102 collected health system data in several ways. First, the probability of freedom
103 achieved by the surveillance system can be determined at the specified DP over
104 the period since negative reporting has occurred. [15] For example, the freedom
105 methodology was used to confirm the absence of porcine reproductive and
106 respiratory syndrome in Sweden using passive surveillance data with an
107 estimated 99.8% probability of FFI. [24] Applying this to malaria, assuming that
108 our population consists of the catchment area of a health facility and that our
109 unit sensitivity (USE) is 0.05 (a number that will be highly variable in practice),
110 after three years of monthly zero reporting we can be 99% confident that, if
111 malaria is present, there are fewer than 3 infections (i.e. the preset DP) in the
112 population, if they exist (figure 1A – example corresponds to the light blue line).
113 The freedom calculation according to passive case detection is dependent on USE
114 and can either be estimated for each time point, here assumed to be monthly
115 following typical health system reporting, or assumed to be static over time (as
116 was the case here). USE is typically estimated according to a scenario tree model,
117 using either parameters for each branch according to available data or if
118 unknown, parameters can be derived using stochastic modeling to account for
119 uncertainty (see box 1 for tree structure and parameters used) [14, 34]. Results
120 can be used to identify the likelihood of having achieved elimination per health
121 facility or to identify facilities that have yet to achieve the desired probability of
122 freedom and should therefore be targeted for improvements in reporting or
123 surveillance activities. The data from each facility in the surveillance network
124 can also be aggregated to generate an overall FFI estimate for the region.
125

126 If the level of confidence achieved within the desired time or the DP attained is
127 not sufficient, the number of additional months of negative reporting required
128 can be determined. For example, 5 years of negative monthly reporting would be
129 required to achieve a 99% probability of freedom at a DP of 2 malaria infections
130 (figure 1B – example corresponds to the purple solid line). The current malaria
131 elimination guidelines specify that there should be three years of negative
132 reporting. It follows that the DP that can realistically be achieved in that time, the
133 time required for the desired level of confidence to be attained, (figure 1B –
134 corresponding to the dark blue line) as well as identifying the USE required to
135 achieve the desired DP within the three year timeline can be calculated. [15] For
136 example, to achieve a 99% probability of freedom from infection with a DP of 1
137 within 3 years, a system sensitivity of 15% must be maintained (figure 1C –
138 example corresponds to the dark green line). These estimates would then be
139 used to inform evidence-based guidelines for confirming malaria elimination
140 that are biologically and operationally tractable by the passive case detection
141 system alone.

142

143 *Active Case Detection*

144 Where PCD alone is insufficient to achieve acceptable estimates of FFI, actively
145 collected data can be used to increase the surveillance sensitivity. [7] For
146 example, active screening of pigs was conducted to establish the elimination of
147 foot-and-mouth disease in the Luzon region in the Philippines. [25] Actively
148 collected data is common in many malaria control programs including the use of
149 large-scale household malaria indicator surveys (MIS). [26-29] The FFI
150 methodology can assist in survey design with the aim of looking for infections

151 when none are expected. [19] The results can then be used to estimate the
152 probability of FFI according to the surveillance sensitivity achieved through the
153 active screening or combined when routine surveillance data alone are
154 insufficient to achieve the desired sensitivity. For example, Cruz et al conducted a
155 cross-sectional serological survey to supplement evidence of freedom from
156 equine infectious anemia virus infection in Spanish purebred horses. [30]

157

158 Working with the assumption that the objective is to detect the presence of
159 infections if the true prevalence in the population is equal to or exceeds the DP,
160 the required sample sizes to achieve the desired level of surveillance sensitivity
161 assuming simple random sampling can be calculated. Furthermore, as livestock
162 tend to cluster in farms and pens or cages within farms, sample size calculations
163 for clustered populations have also been developed. [18, 31] These calculations
164 are highly applicable for malaria and the two-stage clustered design is often used
165 for MIS's where no accurate sampling frame of people or households exists. [32]
166 For example, using a representative two-stage random sampling design and
167 assuming a large population, to achieve 85% surveillance sensitivity 421 clusters
168 with 25 people per cluster are required, to detect 1 infected cluster per 200
169 clusters (figure 2 – example corresponds to the red dashed line). This is only
170 slightly larger than the sample sizes used for MIS to ascertain infection
171 prevalence. [27, 28]

172

173 An additional element developed as part of the freedom toolbox is the use of
174 risk-based sampling. Briefly, instead of taking a representative sample of the
175 population, detecting the presence of infection becomes more efficient by

176 randomly sampling those animals or people that are most likely to be infected.
177 [14] In terms of malaria, if the populations that are at higher risk of having a
178 malaria infection (e.g. migrant populations or school-aged children) can be
179 identified and oversampled as part of the surveillance activities, the likelihood of
180 detecting an infection increases and the same sensitivity can be achieved with a
181 smaller sample size as compared to representative sampling. [14, 33] For
182 example, if a population with 5 times greater risk of infection is targeted, for
183 example the population around known malaria vector breeding sites, to achieve
184 a 85% surveillance sensitivity with a DP of 1 infected cluster per 200 clusters,
185 only 199 clusters with 25 people per cluster would have to be sampled using a
186 risk-targeted design (figure 2 – example corresponds to the red dashed line).
187 This is over a 50% reduction in sample size compared to representative
188 sampling. If the populations can be identified and risk quantified, the risk-
189 targeted approach is likely to become an accepted approach as malaria
190 transmission becomes more heterogeneous and conventional MIS less sensitive.

191

192 Similar to data generated with PCD, evidence generated through freedom
193 surveys can be accumulated over time with the probability of achieving FFI being
194 updated at each time-step, discounting the likelihood of re-introduction. This
195 means that smaller annual surveys in the target population (e.g. schools) can
196 achieve the same sensitivity as a single large freedom survey. [20]

197

198 *Complex Surveillance Systems*

199 As in the veterinary domain, information from multiple sources of passive and
200 active malaria surveillance are commonly available and can be combined in

201 determining FFI. [17, 34] The scenario tree modeling used to estimate USe of
202 passive surveillance systems can be extended to estimate the sensitivity of each
203 component, or source of information contributing to the surveillance system
204 (figure 3A). Components can then be combined to provide an overall estimate of
205 the surveillance sensitivity and FFI, after subtracting any potential overlap. By
206 calculating the sensitivity of each component separately, the strength of the
207 component based on the quality and weight of evidence is accounted for in the
208 resulting overall sensitivity estimate according to how the components are
209 combined. [14, 34] For example, this combined approach has been used in
210 estimating FFI of porcine reproductive and respiratory syndrome in Sweden.
211 [24] Components common in malaria surveillance could include routine health
212 system reporting, active household screening for malaria by community health
213 workers and active household surveys conducted through research activities or
214 MIS. [29, 35] The sensitivity of each component can be calculated and combined
215 to estimate the probability of FFI accounting for all available data (figure 3B).
216 [17]
217
218 Although these models are sometimes difficult to parameterize, the scenario tree
219 approach offers the flexibility to adapt to the structure of the surveillance system
220 of interest. [14] When constructing the scenario trees, the parameters can be
221 associated with distributions and stochastic modeling used to account for any
222 uncertainties. This is described in detail by Martin et al. [34] This tool could
223 provide a mechanism to compare systems and identify areas for improvement.
224 Also, by identifying the tree branches with low probabilities the use of scenario
225 trees could inform what areas of the surveillance system could be targeted for

226 improvement to achieve the desired system sensitivity. [17] The scenario tree
227 modeling approach can also provide a benchmark with which to gauge the ability
228 of the system to detect the disease of interest.

229

230 **Concluding Remarks**

231 The optimum methods for confirming that a region is free from malaria infection
232 would ideally be both flexible to account for the significant microepidemiological
233 variation present in transmission while providing a consistent standard to
234 monitor achievements by programs. The FFI concepts presented here offer a set
235 of well-established methods on which such specific, yet flexible guidelines can be
236 based to support the malaria elimination certification process required by the
237 WHO. [36] Despite the heterogeneity in malaria ecology and transmission
238 potential, consistent thresholds for the DP and acceptable probability of freedom
239 can be established based on the biology of the malaria transmission and
240 acceptable levels of uncertainty, greatly simplifying the implementation of these
241 tools. The pressing need would be to determine and quantify a standardized set
242 of surveillance tree branches to estimate USe for each type of surveillance
243 system as well as how to combine the components. Quantifying the risk of re-
244 introduction of infections and determining at what spatial scales re-introduction
245 can and should be estimated are also important steps towards being able to
246 effectively apply this methodology. [7]

247

248 In an era of accelerating the timelines toward elimination new analytical
249 approaches for defining surveillance for negative reporting are required. [37]
250 Despite the concepts of the FFI being relatively simple and intuitive, they have

251 yet to be investigated for human health surveillance. Developing tools analogous
252 to FFI for malaria surveillance data will be needed before achievable and
253 evidence-based thresholds and guidelines can be determined (see Outstanding
254 Questions). Appropriately repurposed, FFI tools could be used to provide robust
255 evidence that the lack of cases being reported through the passive and/or active
256 surveillance systems suggests that malaria elimination has been achieved. The
257 FFI tools provide novel methods that should be validated for malaria and other
258 human disease systems to ensure that there is sufficient confidence in achieving
259 elimination. A logical extension is the potential to provide evidence to inform the
260 requirements for certification of malaria elimination, a major goal for many
261 endemic countries.

262

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269

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366

367 **Author Contributions**

368 Conceived the paper: GS; Conducted the analysis: GS, AC; Wrote the first draft of
369 the manuscript: GS; Contributed to the writing of the manuscript: GS, CD, AC;
370 Agree with the manuscript's results and conclusions: GS, AC, CD. All authors have
371 read, and confirm that they meet, ICMJE criteria for authorship.

372

373 **Boxes:**

374 **Box 1: Assumed parameters for illustrating the freedom tools.**

- 375 - The prior probability of freedom is 0.5 - a conservative estimate suggesting
376 that ongoing transmission and having achieved elimination are both equally
377 likely;
- 378 - There is minimal risk of re-introduction of infections meaning that an
379 infection is imported and transmission re-established in the population
380 ($p=0.001$);
- 381 - The sensitivity of the surveillance system and the probability of detecting an
382 infected individual does not vary over time;
- 383 - The branches used in the scenario tree model to derive USE were the
384 probability that an infection is symptomatic (0.5), they seek care (0.5), the
385 clinician suspects malaria (0.3), they are tested for malaria (0.8) and the
386 diagnostic test identifies the infection (0.95). These figures and were used as
387 an example only and are not meant to be representative of a specific
388 environment.
- 389 - The diagnostic test sensitivity could be the result of a single test or multiple
390 tests conducted in series or in parallel;
- 391 - The diagnostic test specificity is 1.0 which could be the result of a perfect test
392 or because any positives are followed up and re-tested to confirm that they
393 are in fact false positive readings as is standard practice in an operational
394 context and therefore is a valid assumption however, formulae are available
395 to incorporate imperfect test specificity;
- 396 - The population represents a single health facility catchment area.

397 - All of the above parameters can and should be adjusted according to the
398 specific scenarios where it is applied.

399

400 **Figure Legend**

401

402 **Figure 1:** Calculated probability of freedom from infection illustrating concepts
403 and applicability for decision-making. A) Estimated probability of freedom from
404 infection calculated assuming monthly reporting and a unit sensitivity of 0.05 for
405 different thresholds for the number of infections to detect The red vertical
406 dashed line corresponds to the probability of freedom achieved after 3 years of
407 negative reporting as is specified in the current guidelines for certifying malaria
408 elimination while the horizontal red dotted line represents the 0.99 probability
409 of freedom threshold. B) The probability of freedom achieved after 3 (blue), 5
410 (purple), and 10 (aqua) years according to different levels of design prevalence
411 and a unit sensitivity of 0.05. C) The probability of freedom from infection
412 achieved over monthly time steps assuming a design prevalence of 1, calculated
413 according to surveillance system sensitivities ranging from 0.01 (dark blue) to
414 0.20 (orange). The red vertical dashed line corresponds to the probability of
415 freedom achieved at 3 years while the horizontal red dotted line represents the
416 0.99 probability of freedom threshold. Details on methodologies and the
417 generation of curves are available in the FAO guidelines [14] as well as the
418 RSurveillance R package.

419

420 **Figure 2:** Sample size calculations for active surveillance to support freedom
421 from infection estimates. Sample sizes required for two-stage clustered sampling

422 designs assuming a representative random sample (blue) and a risk-targeted
423 approach assuming 80% of your sample is targeting the 20% of clusters with 5
424 times higher risk (red) to achieve 85% surveillance sensitivity. The red dashed
425 line corresponds to the sample size required to detect 1 infected cluster per 200
426 clusters. Details on methodologies and the generation of curves are available in
427 the FAO guidelines [14] as well as the RSurveillance R package.

428

429 **Figure 3:** Applying the freedom from infection tools to account for multiple
430 streams of surveillance data. A) Example of a simple scenario tree modeling for
431 estimating the surveillance sensitivity of each component. Probabilities are
432 assigned at each branch point and stochastic modeling can be used to account for
433 uncertainty in the parameter estimates. In this example age is a risk factor for
434 the probability of infected individuals having clinical malaria and being identified
435 as positive according to clinical decision making whereas traveling is a major
436 risk factor for contracting malaria in those sampled as part of community based
437 surveys; adapted from Martin et al 2007 [17]; B) Probability of freedom achieved
438 by combining active and passive surveillance data. The sharp increase in the
439 curves that occur at month 0, 12, and 24 represent the boost in surveillance
440 sensitivity due to freedom surveys whereas the gradual increase in the
441 probability of freedom in between active surveys corresponds to the
442 contribution of routine surveillance. The different colored curves correspond to
443 freedom surveys designed according to achieve different survey sensitivities
444 with a greater sample size required to achieve a higher survey sensitivity. The
445 sensitivity of the passive surveillance system reporting between survey time
446 points was assumed to be 0.05. The probability of freedom is discounted by the

447 probability of disease re-introduction over time. Details on methodologies and
448 the generation of curves are available in the FAO guidelines [14] as well as the
449 RSurveillance R package.

450

451 **Glossary:**

452 **Cluster:** A group of individuals that are epidemiologically related and are
453 considered to be a distinct primary sampling unit (e.g. a political unit, health
454 facility or school catchment area etc.) in the context of designing an active
455 surveillance program

456 **Design Prevalence (DP):** The hypothetical level of infection against which the
457 system is evaluated and is considered to be the number of cases to detect so that
458 transmission is not likely sustained below this level.

459 **Prior Probability of Freedom:** The assumed probability of population freedom
460 prior to undertaking the surveillance being analyzed.

461 **Probability of Freedom from Infection:** The probability that the population is
462 “free” from infection (at the design prevalence) given the negative surveillance
463 results and is analogous to the negative predictive value of the surveillance
464 system. In this context “free” is defined as either eliminated or present at a
465 prevalence less than the specified design prevalence.

466 **Surveillance System Sensitivity (SSe):** The probability that the surveillance
467 system would detect one or more infected individuals if the population is infected
468 at or above the design prevalence and is calculated as: $1 - (1 - USe)^{DP}$

469 **Unit Sensitivity (USE):** The probability that an individual with the infection will
470 be detected by the surveillance system and is typically estimated according to

471 scenario tree modeling and is the product of the tree branches representing the
472 flow of an infected individual through the system.

473

474 **Outstanding Questions Box:**

475 - What is the acceptable design prevalence to use for malaria and should it be
476 consistent or allowed to vary based on microepidemiological characteristics?

477 - What is the acceptable probability of freedom that should be sustained for
478 what amount of time for an area to be considered free from infection?

479 - Are the sample size calculations for freedom surveys designed for use in
480 veterinary epidemiology sufficient to detect malaria infections if it is present
481 at or above the stated threshold?

482 - How should data generated through multiple surveillance streams be
483 combined?

484 - Does scenario tree modeling accurately quantify the sensitivity of a passive
485 surveillance system?

486 - Which branches in the scenario trees are required and how can the
487 probabilities associated with these branches be accurately quantified.

488 - What information is essential to collect before malaria is eliminated to
489 inform effective implementation of the freedom methodologies?

490

491

492

493

494 **Supplementary File 1: Overview of Freedom From Infection Methodology**

495

496 The key concepts and formulae associated with this work are presented here.

497 For additional details including the broader literature on health surveillance

498 systems, metrics associated with diagnostic tool performance, probability theory

499 readers are encouraged to refer to the supporting literature. This text has been

500 adapted from documentation prepared by Martin et al [1] and from the FAO [2]

501 to highlight the mathematical formula associated with the concepts presented in

502 the accompanying manuscript on freedom from malaria infection.

503

504 ***Freedom From Infection - Concept:***

505

506 The hypothesis of freedom from infection being tested is:

507

508 H₀: The area is infected at a level at or above the stated design prevalence

509 H_A: The area is free from the infection or the level of infection is below the stated

510 design prevalence

511

512 Probability of freedom is therefore the probability that the area is free from

513 disease, given that the surveillance did not detect any infected individuals. Using

514 Bayes theorem, we can calculate the probability of freedom as:

515

516
$$P(\text{free}) = \frac{\text{True Negative}}{(\text{True Negative} + \text{False Negative})} \quad \text{Equation 1}$$

517

518
$$= \frac{(1-P) \times Sp}{(1-P) \times Sp + P \times (1-Se)}$$

519

520 Where:

521 Sp and Se are the sensitivity and specificity of the surveillance system, and

522 P is the prior probability that the country was infected

523

524 The prior probability (P) that infections exist in an area will significant influence

525 the resulting P(free) estimates. Unless a strong evidence base is available to

526 suggest otherwise, the acceptable value for P is 0.5 for the first round of negative

527 surveillance providing a conservative prior and suggesting that both infections

528 and freedom are equally likely. This prior is then updated at each time-step of

529 surveillance reporting based on the P(free) result obtained at the previous time

530 period.

531

532 ***Disease re-introduction:***

533 As negative surveillance results accumulate over time increasing the certainty in

534 achieving freedom. However, historical data decreases in value, depending on

535 the risk of re-introduction of new infections that would change the infection-free

536 status of the population. When the risk of introduction of disease is small, older

537 information retains more of its value and vice versa. To account for the risk of re-

538 introduction of infections into a population, the p(freedom) calculation is

539 adjusted as:

540

541 $P(\text{free}) = (1 - P_{\text{free}_{tp-1}}) + P_{\text{Intro}_{tp}} - P_{\text{Intro}_{tp}}(1 - P_{\text{free}_{tp-1}})$ Equation 2

542

543 Where:

544 P_{free} is calculated as in equation 1

545 P_{Intro} is the probability that infection is re-introduced into the area and
546 transmission is resumed, and

547 tp is the surveillance time point being assessed (with $tp-1$ representing the
548 previous time period)

549

550 ***Surveillance System Sensitivity:***

551 Passive Surveillance:

552 The probability that the surveillance system (S_{Se}) would detect one or more
553 infected individuals if the population is infected at or above the DP and is
554 calculated as:

555

556 $S_{Se} = 1 - (1 - U_{Se})^{DP}$ Equation 3

557

558

559 Where the U_{Se} is the unit sensitivity or the probability that an infected individual
560 will be detected by the surveillance system and is typically estimated according
561 to scenario tree modeling. The tree approach uses branches to represent the
562 steps related to the detection of an infected unit with the probability that the
563 individual will transition to the next level assigned to each branch (e.g. the
564 probability of being symptomatic, seeking care, is a suspected case, tested for the
565 disease and the test correctly identifies the infection). The sensitivity that that

566 individual will be detected is the product of the probabilities assigned to each
567 branch. Probabilities can be quantified using available data, expert opinion, or
568 stochastic modeling to account for uncertainty if unknown.

569

570 Active Surveillance:

571

572 The sensitivity of a survey is the probability that, if the population is infected at a
573 given DP, at least one infected individual will be detected. The more people that
574 are sampled, the greater the probability that an infected individual will be
575 detected and therefore sample size for a desired level of surveillance sensitivity
576 can be determined.

577

578 Assuming simple random sampling, imperfect diagnostic test sensitivity and
579 specificity, and large population sizes:

580

581 Survey Sensitivity = $1 - [1 - ((DP \times Se) + ((1 - DP) \times (1 - Sp)))]^n$ Equation 4

582

583 Where DP is the expected number of infections to be detected,

584 Se is the diagnostic test sensitivity (note, if this is 1, this term drops out),

585 Sp is the diagnostic test specificity (note, if this is 1, this term drops out), and

586 n is the required sample size to achieve the desired sensitivity

587

588 For extensions of sample size formula for two-stage cluster and risk-targeted
589 sampling designs see Cameron and Baldock [3] and [4]

590

591 References:

592

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594 stochastic scenario tree modelling: Guide to methodology. Australian Biosecurity
595 Cooperative Research Centre for Emergine Infectious Diseases. Danish
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597

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604

605 4 Cameron, A.R. and Baldock, F.C. (1998) A new probability formula for surveys
606 to substantiate freedom from disease. *Prev Vet Med* 34, 1-17

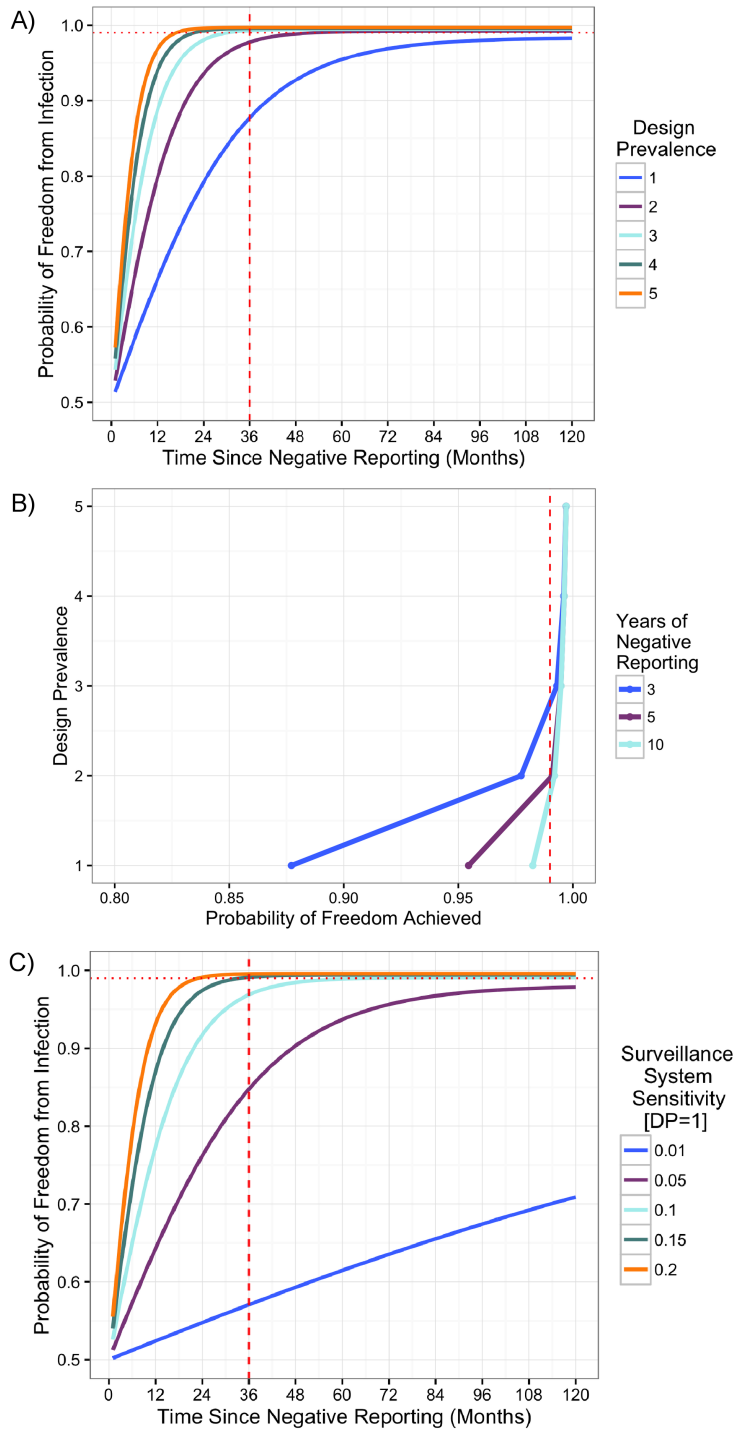
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610 **Figure 1**

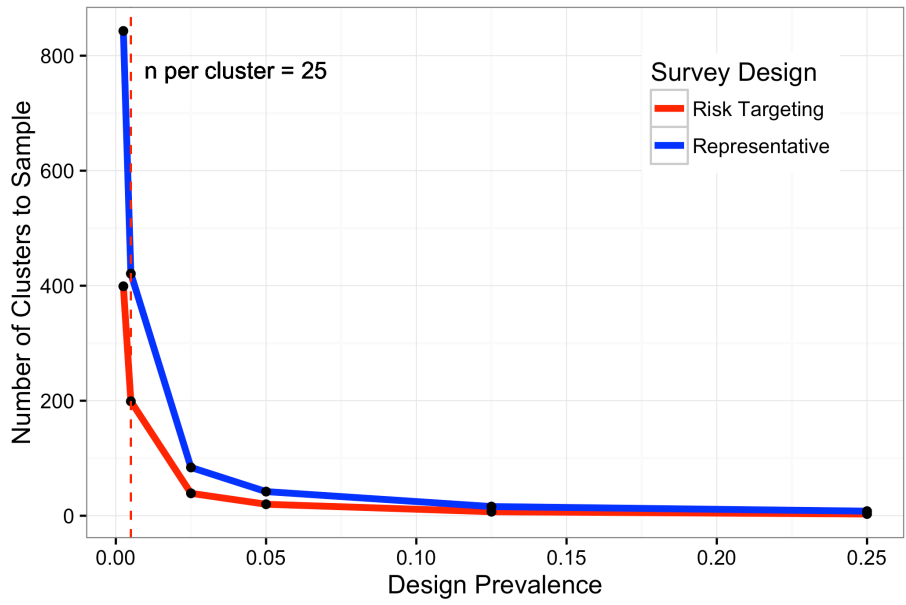
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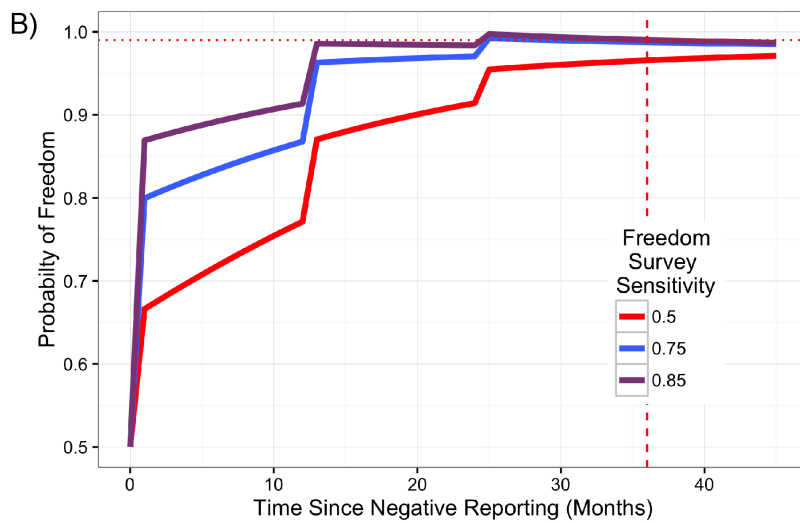
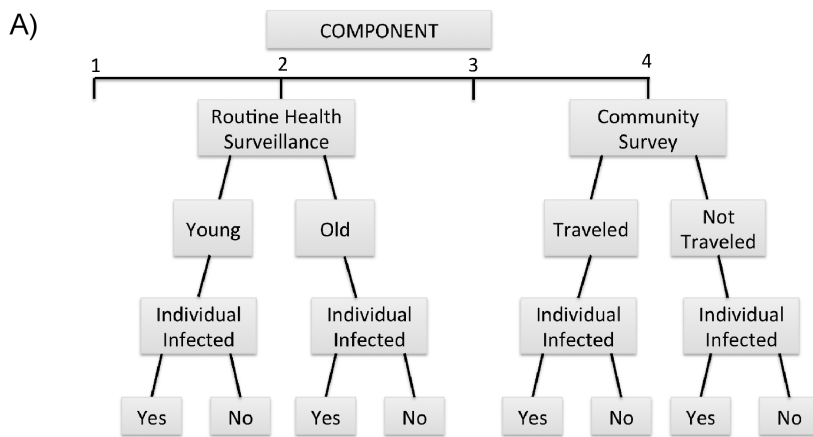
615 **Figure 2**



616

617

618 **Figure 3**



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620