Title: Freedom from Infection: Confirming Interruption of Malaria Transmission

Authors: Gillian Stresman[1*], Angus Cameron[2], Chris Drakeley[1]

* Correspondence: Gillian.Stresman@lshtm.ac.uk (Gillian Stresman)

Affiliations:

1) Department of Immunology and Infection, London School of Hygiene & Tropical Medicine, London, United Kingdom
2) AusVet Pty Ltd., Canberra, Australia

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Abstract

The global reductions in disease burden and the continued spread of drug and insecticide resistance make malaria elimination both viable and imperative, although this may be more easily achieved in some settings compared to others. Whilst the focus has been on optimal approaches to achieve elimination, less attention has been paid to how to measure the absence of malaria. Measuring the absence of transmission poses a specific challenge in that it involves proving a negative. The concept of freedom from infection, routinely used in veterinary epidemiology, can provide quantitative and reproducible estimates that if infections were present above a predefined (low) threshold, they would be detected with a known uncertainty. Additionally, these methods are adaptable for both passively and actively collected data as well as combining information

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

Measuring Elimination

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

Measuring elimination or the absence of disease/infection/transmission poses a specific challenge in that it involves proving a negative. [9, 10] Proving that infection is present in a population is relatively straightforward, as a single positive case would falsify the hypothesis that no infection is present. Conversely, measuring the absence of infection with routine statistical methods is impractical unless the complete population is sampled with a perfect diagnostic tool. [11, 12] Veterinary epidemiologists routinely face the challenge of 'proving zero' to avoid importation of diseased animals as part of the global trade in livestock. [13] The freedom from infection (FFI) methodology was developed to quantify the probability that disease would be detected if it exists in populations (e.g. farms, herds or flocks) of interest. [14] These established methods provide a set of tools for measuring the probability of having achieved elimination whose concepts are highly applicable and should be explored for use in malaria and other human disease systems.

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

Measuring Zero - Freedom from Infection

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

state with a level of confidence that the disease of interest has been eliminated. For a more detailed overview of the FFI methodology, readers are referred to supplementary file 1 and the standard text in veterinary epidemiology. [14]

Freedom Tools in Practice

To our knowledge, the freedom tools have only been fully applied to human health in one instance. Using historical surveillance data, Watkins et al. calculated the sensitivity of the surveillance system to detect wild poliovirus in Australia and calculated the corresponding estimate of FFI. [21] A similar approach to design elimination programs has been employed for other human diseases. For example, the transmission assessment surveys used in the lymphatic filariasis elimination campaigns used a probabilistic mathematical modeling approach to determine the levels of disease prevalence whereby below this threshold, disease is most likely to die out, leading to elimination. [22, 23] However, there has yet to be any evidence that this approach will lead to disease elimination in the field or if it can be transferred to other disease systems. With elimination of malaria and other infectious diseases a global priority, the available and highly relevant FFI framework should be explored.

The following examples are generating using the RSurveillance package for R (v 3.2.3) with the assumptions and parameters used outlined in box 1 (R code available upon request). All parameters can and should be changed to reflect the specific epidemiological setting in the region of interest.

Passive Case Detection

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

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

Active Case Detection

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

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

Concluding Remarks

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

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

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

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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.

Boxes:

Box 1: Assumed parameters for illustrating the freedom tools.

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

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

Figure Legend

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

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

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

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

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

Glossary:

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

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

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

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

Surveillance System Sensitivity (SSe): The probability that the surveillance system would detect one or more infected individuals if the population is infected at or above the design prevalence and is calculated as: 1 – (1 – USe)^(DP)

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

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

Outstanding Questions Box:

- What is the acceptable design prevalence to use for malaria and should it be consistent or allowed to vary based on microepidemiological characteristics?
- What is the acceptable probability of freedom that should be sustained for what amount of time for an area to be considered free from infection?
- Are the sample size calculations for freedom surveys designed for use in veterinary epidemiology sufficient to detect malaria infections if it is present at or above the stated threshold?
- How should data generated through multiple surveillance streams be combined?
- Does scenario tree modeling accurately quantify the sensitivity of a passive surveillance system?
- Which branches in the scenario trees are required and how can the probabilities associated with these branches be accurately quantified.
- What information is essential to collect before malaria is eliminated to inform effective implementation of the freedom methodologies?

Supplementary File 1: Overview of Freedom From Infection Methodology

The key concepts and formulae associated with this work are presented here. For additional details including the broader literature on health surveillance systems, metrics associated with diagnostic tool performance, probability theory readers are encouraged to refer to the supporting literature. This text has been adapted from documentation prepared by Martin et al [1] and from the FAO [2] to highlight the mathematical formula associated with the concepts presented in the accompanying manuscript on freedom from malaria infection.

Freedom From Infection – Concept:

The hypothesis of freedom from infection being tested is:

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

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

Probability of freedom is therefore the probability that the area is free from disease, given that the surveillance did not detect any infected individuals. Using Bayes theorem, we can calculate the probability of freedom as:

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

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

Where:

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

P is the prior probability that the country was infected

The prior probability (P) that infections exist in an area will significant influence the resulting P(free) estimates. Unless a strong evidence base is available to suggest otherwise, the acceptable value for P is 0.5 for the first round of negative surveillance providing a conservative prior and suggesting that both infections and freedom are equally likely. This prior is then updated at each time-step of surveillance reporting based on the P(free) result obtained at the previous time period.

Disease re-introduction:

As negative surveillance results accumulate over time increasing the certainty in achieving freedom. However, historical data decreases in value, depending on the risk of re-introduction of new infections that would change the infection-free status of the population. When the risk of introduction of disease is small, older information retains more of its value and vice versa. To account for the risk of re-introduction of infections into a population, the p(freedom)calculation is adjusted as:

P(free) = $\left(1 - Pfree_{tp-1}\right) + PIntro_{tp} - PIntro_{tp}(1 - Pfree_{tp-1})$ Equation 2

Where:

Pfree is calculated as in equation 1

PIntro is the probability that infection is re-introduced into the area and transmission is resumed, and

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

Surveillance System Sensitivity:

<u>Passive Surveillance:</u>

The probability that the surveillance system (SSe) would detect one or more infected individuals if the population is infected at or above the DP and is calculated as:

SSe = $1 - (1 - USe)^{DP}$ Equation 3

Where the USe is the unit sensitivity or the probability that an infected individual will be detected by the surveillance system and is typically estimated according to scenario tree modeling. The tree approach uses branches to represent the steps related to the detection of an infected unit with the probability that the individual will transition to the next level assigned to each branch (e.g. the probability of being symptomatic, seeking care, is a suspected case, tested for the 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 = $1 - [1 - ((DP \times Se) + \big((1 - DP) \times (1 - Sp)\big))]^n$ 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

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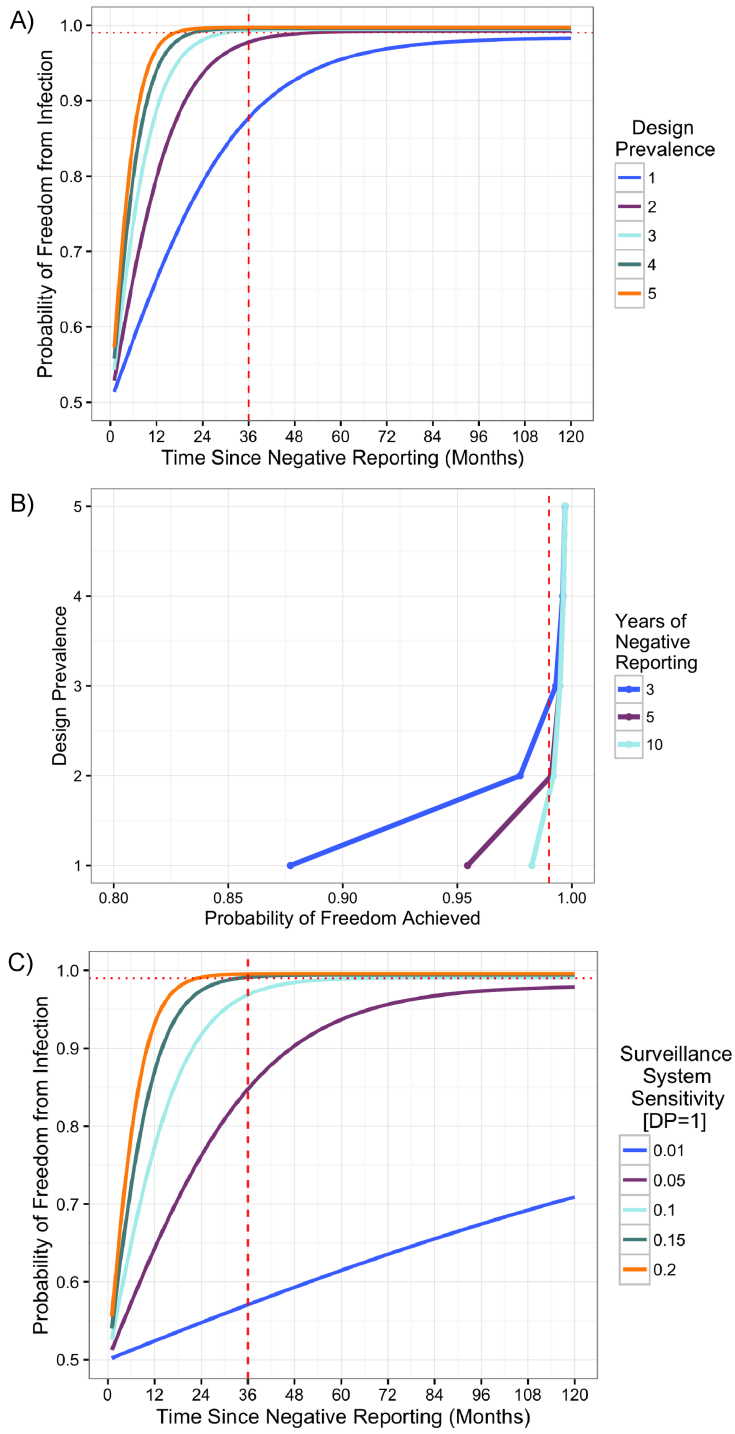
Figure 1



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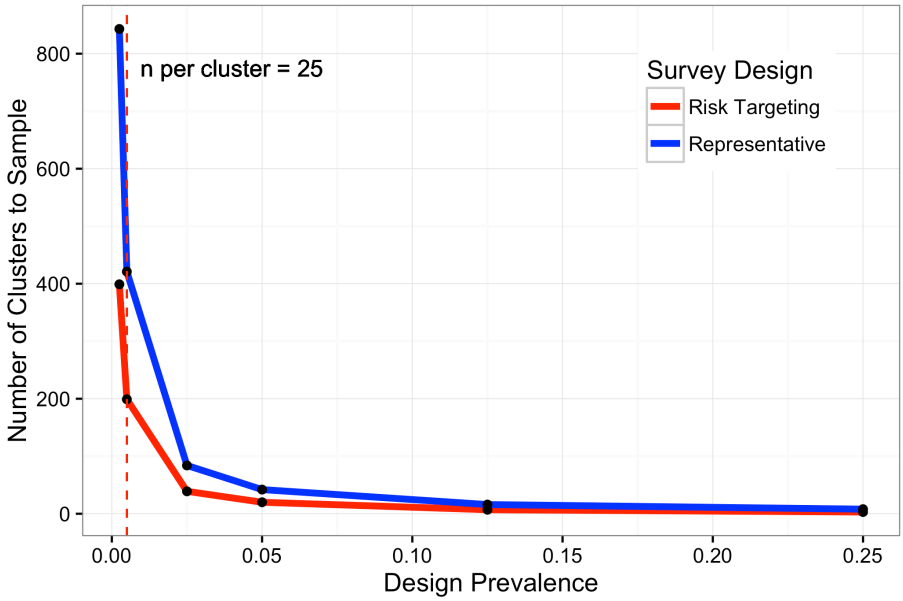
615 **Figure 2**



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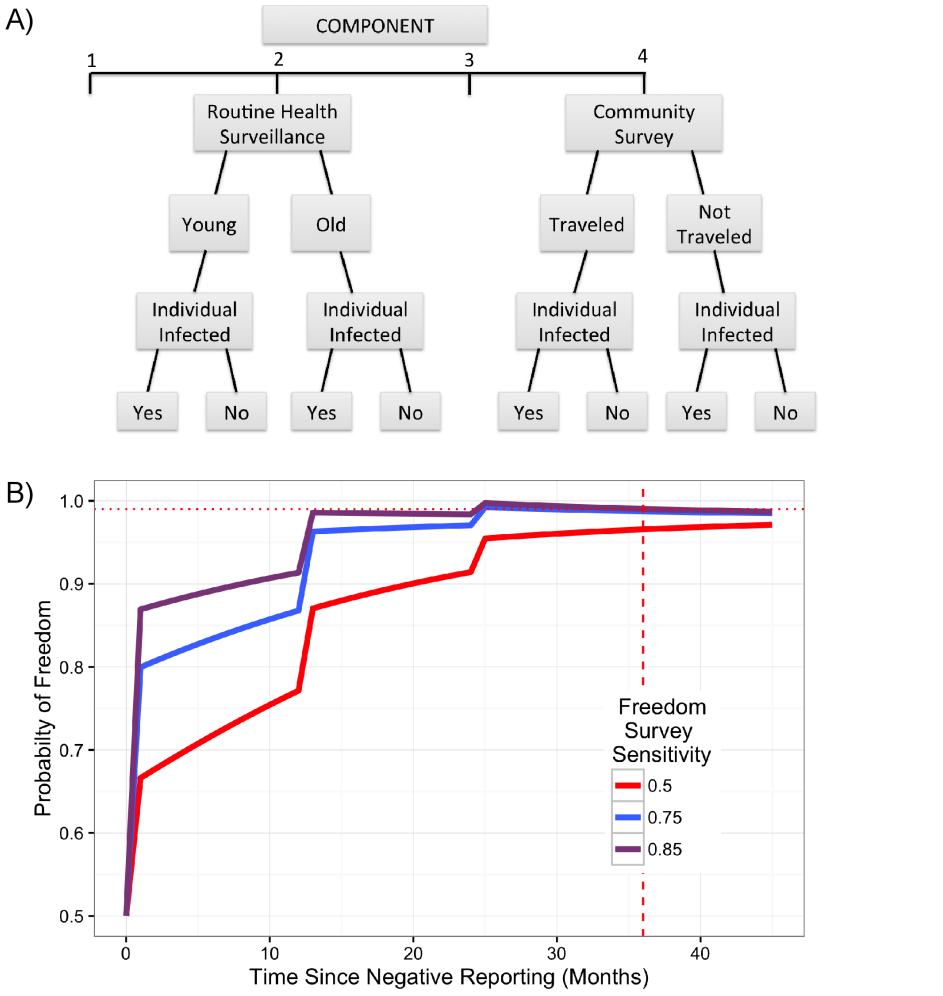
618 **Figure 3**



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