Trends in Parasitology

CellPress

Opinion

Freedom from Infection: Confirming Interruption of Malaria Transmission

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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

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Evidence-based approaches for informing public health decision-making in the context of disease elimination are currently lacking.

Tools developed in veterinary epidemiology can generate quantitative and reproducible estimates for the probability of detecting disease were it present at a pre-specified (low) level.

Passive case detection can be augmented with actively collected data to generate an overall estimate of the sensitivity of the surveillance system and corresponding estimates of freedom from infection.

Historical data can be incorporated into estimates of freedom with appropriate weighting according to the probability that infection is introduced into the population.

For malaria control programs that are reorienting surveillance for elimination certification, freedom from infection estimates provide a potential standardized approach for informing decision-making.

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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 predetermined 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 predetermined 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 reintroduction, 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 Box S1 in the supplemental information online, 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.

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 reintroduction 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 are 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 retested 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.

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.