Measuring the path toward malaria elimination

Rigorous and achievable targets and milestones can be developed from standard malaria surveillance data.

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In many parts of the world, malaria elimination—defined by the World Health Organization (WHO) as the absence of locally acquired malaria cases in the country—is being considered as a target because of recent successes in reducing disease burden (1–2). Rigorous evaluation of malaria elimination programs is essential for financial and political support to be maintained. Yet such evaluation remains challenging, and appropriate metrics to ascertain "success" are needed.

Although the long-term focus on elimination is commendable, evaluation of programs cannot rely on a dichotomous approach where "success" would correspond to no locally acquired malaria cases, and anything else would be seen as failure. Evaluation needs to take into account the local and regional epidemiological circumstances, because countries that manage to control local transmission to relatively low levels but receive large numbers of imported cases are likely to see locally acquired cases (*3*). Effective programs may therefore be wrongly perceived as unsuccessful, jeopardizing their long-term viability. In addition to the long term objective of elimination, we must develop intermediate milestones that better capture and acknowledge these scenarios.

Such a milestone should be the interruption of endemic transmission, meaning that the country would eventually see malaria go away if importation ceased. The country could then aim to reduce chains of transmission generated from imported cases down to zero. Although this sounds sensible, there are no operational measures and tools for evaluating local transmission as it approaches elimination, because incidence estimates either require surveillance data with perfect case detection or surveys with impractically large sample sizes (*4*). In addition, incidence does not measure local transmission in the context of importation.

Here, we present simple, theoretically sound, and robust metrics to ascertain progress toward elimination. Aside from their importance for program evaluation, these metrics also allow more-refined assessment of the epidemiological situation, which could lead to more accurate evaluation of different elimination strategies (for example, differentiating between persistent low-level endemic transmission or repeated importation and extinction events that may require different public health approaches).

HAS ENDEMIC TRANSMISSION BEEN HALTED? The term "controlled nonendemic malaria" describes areas where interventions have interrupted endemic transmission but where some local transmission from imported cases remains (*3*). The reproduction number *R* (average number of new persons infected by a person with malaria given current control interventions) would be a theoretically sound measure to ascertain controlled nonendemic malaria (as $R < 1$ indicates that transmission cannot be self-sustaining locally) (*3*). However, these considerations have had limited practical impact because (i) it is not possible to directly measure *R* in the field, because chains of transmission are typically not observed; and (ii) estimates of *R* derived from mathematical models require local information, which is seldom collected.

To overcome these issues, we propose a method to test the hypothesis $R \geq 1$ that only requires standard data (the numbers of local and imported malaria cases detected by surveillance). The approach uses a simple criterion—Is the proportion of imported cases among detected cases above a certain threshold?—to determine the status of controlled nonendemic malaria. The approach accounts for factors such as incomplete case detection and considers a worst-case scenario to ensure that the test for $R \geq 1$ is conservative. Last, it can easily be tuned to consider more stringent milestones, for example $R < 0.5$, in which imported cases cause shorter chains of transmission and the disease is closer to local elimination. A description of the method and a user-friendly tool can be found in the supplementary material (SM).

Given the number (*n*) of malaria cases detected by surveillance, the proportion of cases that must be imported to provide statistical evidence that controlled nonendemic malaria has been reached (i.e., reject the hypothesis that $R \geq 1$) is shown in the figure on the left (Fig. 1). This proportion is 48% when $n = 50$ but drops to 32% when *n* reaches 500 cases (see also table S1).

We apply this approach to Swaziland, a country that embarked on an elimination campaign in 2008 (*5*). Malaria is a notifiable disease (required by law to be reported) in Swaziland. Since 2009, all cases confirmed by a rapid diagnostic test and/or microscopy are reported to a central database. An investigation of 64% of confirmed cases was carried out, and travel history was ascertained, with those reporting travel to endemic regions within the previous 2 to 8 weeks classified as imported cases. Cases identified by screening people associated with cases identified by routine surveillance were omitted from the analysis to avoid overestimating *R* (see SM) (*6*).

The results from weekly epidemiological reports are shown in the middle of the figure. Thirty-six percent (52 out of 143), 45% (170 out of 377), and 67% (153 out of 229) of investigated cases were imported in 2010, 2011, and 2012, respectively. Thus, the status of controlled nonendemic malaria was reached in 2011 and 2012 but not in 2010 (borderline). This provides evidence that, since 2010, Swaziland has halted endemic transmission at the national level and that malaria would be eliminated if the current level of control was continued and importations ceased. Swaziland has a very effective

malaria surveillance network (*7*), but the approach would remain valid if the case-detection rate (the proportion of malaria cases identified) or the investigation rate (the proportion of confirmed cases where travel history is ascertained) were lower (see SM).

ESTIMATING *R* BY SEASON. Beyond determining whether *R* is beneath a certain threshold, it may be necessary to estimate *R* and its associated uncertainty directly. For example, it may be important to separate *R* estimates for high and low seasons to evaluate the effectiveness of local interventions and to predict their impact in countries with different seasonal patterns. For instances in which there is a good understanding of local surveillance and health systems (e.g., the proportion of malaria cases detected and treated), we built upon recent advances in statistics (*8*) to develop methods to estimate temporal trends in *R* from the epidemic curves of imported and local cases (middle of the figure, see SM). These trends are shown on the right of the figure for Swaziland. The reproduction number *R* was not significantly different from 1 during the high season for 2010 and 2011; but was significantly smaller for 2012. A sensitivity analysis (SM) shows that estimates were robust to changes in the assumed case-detection rates. This method is more precise than the threshold framework presented on the left in the figure, although the model-fitting process makes it less user-friendly.

LIMITATIONS AND FURTHER DEVELOPMENTS. Here, we generated countrywide estimates of *R*. Given the important spatial heterogeneities in malaria transmission, national statistics may mask the presence of more localized pockets of endemic transmission. Further work is needed to determine at which optimal spatial resolution analyses should be carried out (see SM). Our approach was developed for the monitoring of *falciparum* malaria elimination. However, a majority of countries affected by malaria are likely to have cases of *Plasmodium vivax* (*2*). In this species, new cases can be caused by a relapse of a previous infection as well as by local transmission. Our test for $R \geq 1$ remains valid in areas affected by *P. vivax* although power is diminished (see SM).

DO WE NEED TO CHANGE STRATEGY? Our results show that a country in mainland sub-Saharan Africa has halted endemic transmission. The method can also help predict the likely impact of interventions. For $R = 0.5$, 500 imported cases are expected to result in about 500 subsequent local cases before the disease is eliminated. If further investment in vector control could reduce *R* to 0.3, the number of local cases would drop to about 200. In contrast, relaxing control measures, raising *R* to 0.6, would generate longer chains of transmission and a total of 750 local cases. Understanding the current level of transmission might have programmatic implications. For example, when *R* is very low it might be feasible and economically advantageous to reduce routine disease control and concentrate on outbreak investigation

and response.

In endemic countries, estimating *R* may help determine whether malaria elimination is feasible in a particular location by quantifying the current level of local transmission and then using mathematical models to predict what additional control is required to push *R* below 1. For example, if *R* is estimated to be 3 in a particular location and surveys indicate current effective bed-net coverage is 40%, increasing effective bed-net coverage to 60% in that location should be sufficient to reach controlled nonendemic malaria (*9*).

There is little doubt that financial and political support for the malaria elimination agenda will fade out if programs are systematically failing to reach their targets. Instead of just presenting numbers of cases, control programs should report estimates of *R* to better reflect the current level of transmission given their level of disease importation. This will allow a more rigorous evaluation of different elimination strategies to enable the successes of countries like Swaziland to be maintained and replicated elsewhere.

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SUPPLEMENTARY MATERIALS

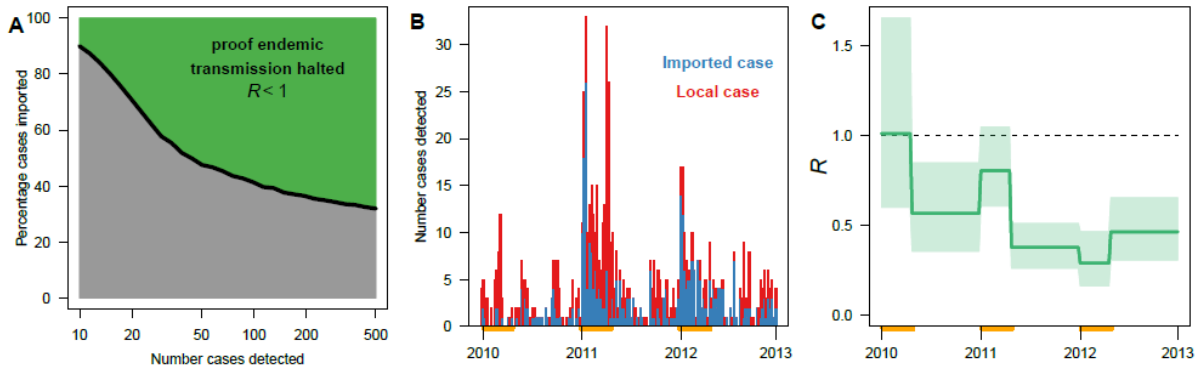

Fig. 1. Tracking malaria transmission. (**Left**) The percentage of imported cases required to confirm that endemic malaria transmission has been halted. If the percentage of imported cases is greater than the solid black line (green area), there is statistical evidence that malaria is no longer endemic. The gray areas show where the hypothesis that $R \geq 1$ cannot be rejected, either because there is insufficient evidence or because endemic transmission is ongoing. (**Middle**) The weekly incidence of malaria cases investigated in Swaziland. All cases are likely to *be* falciparum malaria (*9*). Orange lines on the *x* axis indicate the high-transmission season. (**Right**) Estimates of the reproduction number, *R*, for each season, with shaded area indicating 95% credibility intervals. See SM for details.