Peer Community In Infections

Reaching the last miles for transmission interruption of sleeping sickness in Guinea: follow-up of achievements and policy making using microsatellites-based population genetics

Hugues Nana Djeunga *based on peer reviews by* ***Fabien HALKETT*** *and 2 anonymous reviewers*

Moise S. Kagbadouno, Modou Séré, Adeline Ségard, Abdoulaye Dansy Camara, Mamadou Camara, Bruno Bucheton, Jean-Mathieu Bart, Fabrice Courtin, Thierry de Meeûs, Sophie Ravel (2024) Population genetics of *Glossina palpalis* gambiensis in the sleeping sickness focus of Boffa (Guinea) before and after eight years of vector control: no effect of control despite a significant decrease of human exposure to the disease. bioRxiv, ver. 2, peer-reviewed and recommended by Peer Community in Infections.
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Thanks to the coordinated and sustained efforts of national control programs, the World Health Organization (WHO), bilateral cooperation and nongovernmental organizations, the incidence of Human African Trypanosomiasis (HAT), better known as sleeping sickness, has drastically decreased during the last two decades (WHO, 2023a). Indeed, between 1999 and 2022, the reported number of new cases of the chronic form of sleeping sickness (*Trypanosoma brucei* gambiense) fell by 97% (from 27 862 to 799), and the number of newly reported cases of the acute form of HAT (*Trypanosoma brucei* rhodesiense) fell by 94% (from 619 to 38) (WHO, 2023b). These encouraging trends led the WHO to target this debilitating and highly fatal (if untreated) vector-borne parasitic disease for elimination as a public health problem by 2020, and for interruption of transmission (zero case) by 2030 (WHO, 2021, WHO, 2023a). However, the disease is persisting in many foci, and even some

cases of resurgence have been documented after unfortunate events such as war or pandemics (Moore et al., 1999; Sah et al., 2023. Simarro et al). Although effective control measures, diagnosis and treatment are complex and require specific skills (WHO, 2023), especially in a context which animal reservoirs, including hidden reservoirs, can contribute to the maintenance/persistence of infection (Welburn and Maudlin, 2012; Camara et al., 2021). Vector control therefore appears as a viable alternative to accelerate sleeping sickness transmission interruption, and WHO has identified some critical actions for HAT elimination, including the coordination of vector control and animal trypanosomiasis management among countries, stakeholders and other sectors (e.g. tourism and wildlife) through multisectoral national bodies to maximize synergies (WHO, 2021).

The paper by Kagbadouno and Collaborators (2024) uses microsatellite markers genotyping and population genetics tools to investigate the impact of 11 years of tiny target-based vector control on the population biology of *Glossina palpalis* gambiensis in Boffa, one of the three active sleeping sickness foci in Guinea (Kagbadouno et al., 2012). Although vector control significantly reduced the apparent densities of tsetse flies (and therefore the human exposure to the vector) as well as the prevalence and incidence of the disease in the Boffa HAT focus (Courtin et al., 2015), no genetic signature of vector control was observed as no difference in population size, before and after the onset of the control policy, was found. The authors then provided national programs and implementing partners with indications on the actions to be taken to (i) maintain the achievements of vector control (thus avoiding rebound/resurgence as was experienced in the past (Franco et al., 2014), and (ii) accelerate the momentum towards elimination by for example combining these vector control efforts with medical surveys for case detection and treatment, in line with WHO recommendations (WHO, 2021).

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Reviews

Evaluation round #1

DOI or URL of the preprint: https://doi.org/10.1101/2023.07.25.550445
Version of the preprint: 1

Authors' reply, 11 January 2024

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Decision by Hugues Nana Djeunga, posted 09 December 2023, validated 11 December 2023

Major revisions

The manuscript submitted by Kagbadouno and colleagues entitled "Population genetics of Glossina palpalis gambiensis in the sleeping sickness focus of Boffa (Guinea) before and after eight years of vector control: no effect of control despite a significant decrease of human exposure to the disease" aim to investigate the impact of tiny target-based vector control on the population biology of G. p. gambiensis in Boffa, using microsatellite markers genotyping and population genetics tools. This is an important study in the field of public health.

Based on my evaluation and the reports from three invited independent Reviewers, this manuscript presents a number of issues and limitations that need to be appropriately addressed before being considered for publication in PCI Infections. Below are some of the most important issues:

1. The justification of the study and problem statement are unclear to me. There is no information on the sleeping sickness status in Guinea or the Boffa focus that would have justified a vector control. What

was the impact of vector control? What is the link with animal reservoirs? What is the link with the post-vector control increase of the GPCAG allele in Côte d'Ivoire? Was resistance established in Côte d'Ivoire after vector control or this was just a hypothesis/speculation by the authors? The objective of the study is different between the abstract and introduction sections, and seems not achieved in this study (based on the objective presented in the introduction section).

2. The study design is not clearly presented. It is unclear how vector control was conducted. For example, (i) how many traps deployed on which area, (ii) for how long tiny targets were deployed before being changed (knowing that their efficacy relies on the baited insecticide), (iii) were the traps set at the same position, (iv) what do the authors consider as cohort? …. The study area is not presented in a comprehensive way, and the figure provided is not that informative. These details are useful for the interpretation of the results.

3. There is not enough information in the discussion section on the effect of vector control on population genetics metrics. For example, it is unclear what can be the influence of the areas not covered by the vector control, knowing that flies' dispersion is about 40 km. Also, the conclusion of the manuscript is a hypothesis rather than a real conclusion, and it is unclear why the authors are raising the hidden human and/or animal reservoir in this context.

4. A few minor editing needed to be addressed: (i) please avoid some unusual abbreviations (for example "aka" at line 50, "in minimax" at line 455) …; (ii) the citation of references in the text should be harmonized a follow the guidelines of the journal …

In addition to my comments and suggestions, the reports of three independent Reviewers provide detailed appreciation of the manuscript. If you are able to fully address these points, we would encourage you to submit a revised manuscript to PCI Infections. Once you have made the necessary corrections, please include a cover letter with a point-by-point response to the comments, including a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes. A decision will be made once we have received your revised manuscript.

We look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,

Hugues C. Nana Djeunga, PhD
Recommender,
PCI Infections.

Reviewed by Fabien HALKETT, 22 November 2023

Kaglbadouno and colleagues present a fine population genetics study aimed at testing the effect of a policy control on the population size of the fly responsible for sleeping sickness in a Guinean focus in Boffa.

They exploit the full power of microsatellite loci to test and produce a high quality dataset. On these data they use various methods to calculate effective size, which can be extrapolated to insect density in the study area. Their precise study does not appear to show any difference in population size between samplings performed before and after the onset of the control policy, even though the latter effectively reduced the outbreak of HAT disease in Boffa. The authors conclude their study with a message of prevention, arguing that

the control campaign should not be interrupted prematurely, otherwise the number of cases of the disease will start to rise again as quickly.

The study is sound and the methods employed are robust. The data pre-processing step can be cited as an example. I have no doubts about the conclusions of this study. I have only two major comments to improve the presentation of the context and provide more detail on the population size estimates.

1. The introduction is rather short, a little too short, and could go into some detail about the policy of controlling the insect vector.

2. The different methods of estimating population sizes show wide variations, with temporal methods in particular giving much higher values. I think it's a matter of regret that the authors don't go into more details about these results. The analyses of the various cohorts are aggregated in a single table that presents the mean values over all the samples. This does not allow us to visualize the differences before and after the onset of the control. This result is only stated in one sentence (without reference to the underlying method).
Even if the analysis techniques differ, it seems possible to me to contrast the before/after estimates for each method, including the temporal method, e.g. by distinguishing between pairs of cohort sampled before/after the onset of the control.

Detailed comments:

L38 indicate the number (instead of several that is quite vague).

L38 end of the line, remove the s at genetics, before tools

L66 same grammatical mistake, remove the s at the end of individuals before clones (and I prefer the term clonal lineage ou clonemates)

L62 Please provide more details on this vector control campaign. What does it involve?

L86 Remove the name of the author in the parenthesis (only the date).

L113 two month generation time (without s at month)

117 considered as distinct time sample (rather than separate entities).

L139 described in Berté et al (2019) – brackets around the date only

L145 to keep

L146 population genetic analyses (remove 's' and data).

L153 note that the appropriate level of population delineation (or the test for a lack of population structure) can also be performed using assignment methods (e.g. DAPC analyses). It could be interesting to further cross the Fst based and DAPC method (also considering the slightly positive Fis value, which may indicate a Wahlund effect behind the contribution of null alleles).

L 157 (here and line 187), remove B. S. in the citation of Weir & Cockerham.

L159 add "slightly" before "negative". (not the same order compared to the Fis values obtained in the case of clonal populations).

L172 from different origins (and place in brackets traps… cohorts) to simplify the sentence

L170-176 Concerning this test, I wonder about the effect of the differences in sample size, with "traps" suffering from very low sample size, which can distort estimates (e.g. Barrès et al. 2013). In this case, it is best to apply rarefaction. From Figure 2, it seems it is not the case. What are the mean and range of sample sizes according to the different origins?

L182 brackets around the date only for the reference De Meeûs et al.

L192 tests were one sided (past tense)

L233 here and line : add the references (Fox). Not obvious that you refer to the package R commander when reading quickly.

L243 choose between "measured" or "tested"

L260 what do you mean by infinite. If the distribution is skew with very large value, it would be more accurate to report the median value rather than the mean.

L303 replace TdM by De Meeûs.

L357-358 not clear to me. Loci B3 and pGp24 are two outlier loci (Fis value not explained by null alleles, Figure 4). Please provide more details.

L399: I wonder whether the larger population size of cohort 10 does not reflect an “outbreak” of tsetse flies (doubling compared with other estimates) which would have motivated the control.

L400: I don’t understand why it would not be possible to perform comparisons with the temporal method. You have estimates for each pair of cohorts, so you can compare pairs of cohorts before and after the onset of the control, no?

More generally, I see a discrepancy between the estimates of population size and the variation in pairwise Fst that you present in figure 5. You obtained slightly negative value for all pairs of population that includes cohort 67. Why this signal in population structure does not translate into different population size estimates? For me, it’s a puzzling result that deserves to be discussed.

Table 2: consider the median rather than the mean estimates.

L485 affect the biodiversity is over conclusive. You only test the effect on tsetse fly populations. Please rephrase.

Reviewed by anonymous reviewer 1, 28 September 2023

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Reviewed by anonymous reviewer 2, 27 September 2023

REPORT REVIEW

Download the review