Revisions made by the authors, 2019-05-23

We would like to thank Timothée Vergne and one anonymous referee for their interesting comments and constructive suggestions which helped us improve our manuscript. We have addressed all the points raised in the revised version of the manuscript. We summarize thereafter the main changes made, then provide a point-by-point answer (in blue) to the comments of the referees.

First, we have extended the simulations as suggested by Timothée Vergne to highlight optimal spatial implementation of increased adult mortality when facing limited resources. We have assessed the minimal increase in adult mortality required and which cells to optimally target when only a given percentage of the whole surface can be controlled with the objective to decrease the whole population density below a given threshold (2 or 5% of the initial population before control). As control for tsetse fly control generally occurs over long periods of time, we did not focus here on when to implement spatial strategies, but considered a typical duration of one year. New figures have been added to the manuscript and to the supporting information. A partial targeted control led to a similar decrease in population size than a homogeneous control while maintaining realistic decreases in female life expectancy, but clearly induced a different spatial distribution of remaining individuals who were much more spatially dispersed after a heterogeneous than a homogeneous control.

Second, as suggested by the anonymous referee, we considered the population resurgence after control has stopped. We simulated the population dynamics for one year after control. Starting from comparable population size after control, resurgence was slow both after a homogeneous and a heterogeneous control. After a homogeneous control, resurgence appeared with a 23% yearly growth rate on average over the grid, resurgence being higher in coldest cells with less variable local temperatures which created refuges. After a heterogeneous control, the population growth rate was much lower at the grid scale (1%), but was much more variable in space, refuges now being located at the interface between controlled and uncontrolled zones. Two figures were added to the manuscript to show these new results.

Reviewed by Timothée Vergne, 2019-02-21

This manuscript presents thoroughly a deterministic compartmental model of tsetse fly population dynamic that accounts for a spatially heterogeneous environment (through a regular grid of 900 cells), movement of flies between cells and a density dependence of the fly dynamic. It includes a sensitivity analysis of the model input parameters on population size that demonstrates that the population dynamic is mostly driven by temperature and adult mortality. Simulations were subsequently conducted to simulate the impact of an increase of the adult mortality on the reduction of the population. The paper is strong (but could be stronger), well-written and clear. After a careful read, I am a little bit frustrated as this study ends in the middle of 2 interesting stories: the description of the population dynamic and recommendations for control strategies. Indeed, should you want to assess the effectiveness of control strategies, you can go further by taking the most out of your spatial model and determining the best spatio-temporal combination of adult mortality increase. So far, your paper assesses the effectiveness of a strategy based on a spatially homogeneous control approach. Given the specificities of your model, it would be very elegant to characterise where and when to increase the mortality to maximise the chance to decrease quickly the fly population. My feeling is that the current version of your manuscript tells too much or too little. My suggestion is that either you make it slightly shorter (and remove the last section on evaluation of control strategies) or you make it much stronger by including an optimisation algorithm to assess where and when to do fly control.

We fully agree and the paper now includes an optimization algorithm to assess where to do fly control. See above for a more detailed answer.

Very minor comments: Abstract: management strategies. Done. I missed Table S2 in the main text. Provided first in M&M L169 and wherever it was useful in this section, as well as in the first paragraph of results. L144: cooler instead of lower. Done. L171-172: any reference to justify this? Otherwise it needs to be included in the sensitivity analysis. We refer now to Alderton et al. 2016, a

simulation study where the effect of this scaling factor has been assessed, indicating that a factor of 0.5 induced the most stable population. L174-179: theta needs to be defined. Added. L176: shoudn't F be F1:4+? This was not clear: yes for stage $S_{t,c}$, but not for $\mu_{X,t,c}$ as parameters do not vary with ovarian age. We introduce X as an index for μ as used also in the next equations to make it clearer. L181: fitted "to the" data. Check other occurrences in the text. Done. L218: Unclear, try to reformulate. We changed to: "A 3-year burn-in period was simulated starting with $N_{0,c}=M_{0,c}=0.5k_c$ ($A_{0,c}=k_c$), using reference parameter values (Table S2), and these provided the initial conditions for the pre-control scenario and for the model sensitivity analysis, where population dynamics was simulated over three more years."

Reviewed by an anonymous referee, 2019-02-21

Summary: The manuscript reviewed herein presents an interesting and substantial body of work which is largely technically sound, to the best of my understanding. In addition to a number of, I believe, small technical questions, the bulk of my comments are aimed at helping guide improvements to the writing for clarity. The work has potentially important implications for vector (and disease) control strategies. While the model is very specific to this case, as was the goal, the approach could be followed to investigate the role of environmental heterogeneity on population dynamics and control strategies in other systems.

The only major comment I have is that there needs to be a bit more information and clarity included in the manuscript. There are also technical questions that may or may not require additional work, but I prefer to include these in the order in which they appear. It is most likely they simply require clarification.

1. Abstract: "...patches with the lowest mean temperatures and lowest variations..." should say something like "smallest variations in temperature" or "lowest variation in mean temperatures". Changed as recommended.

2. Abstract: delete "to maximize its efficiency" from the last sentence. Unless I've missed something and "efficiency" was explicitly tested? Done

3. L 14-15: I'm not completely convinced that this is true (maybe distribution, but dynamics?) and the modeling paper cited (which is definitely a great paper to cite elsewhere in this manuscript!) Hartemink et al. 2015 does not appear to be an appropriate citation to support this claim. Our sentence was indeed not clear. In Hartemink's paper, it is said: "Landscape characteristics are likely to affect the spatial and temporal dynamics of several vector-borne diseases by influencing habitat suitability for vectors and hosts within a suitable climate envelope (Ostfeld, Glass & Keesing, 2005; Lambin et al., 2010). While landscape composition affects the availability and quality of habitat of the different species that interact with the pathogen, landscape configuration and connectivity affect the spatial and temporal probability of contact between vectors and hosts, and are thus significant for understanding pathogen transmission and spread.". In addition, the chosen example (bluetongue) also provides clues on the importance of relating time- and space-varying habitat with population dynamics: "Using the case of bluetongue virus, we illustrate how different landscape configurations may affect transmission risk by differentially promoting interactions between ruminant hosts and midges with diverse breeding habitat requirements". This is why we cited this reference here. We therefore kept it but changed the sentence to make it hopefully clearer: "This is particularly true when it comes to managing vector-borne diseases whose transmission may be affected by landscape configuration as interactions between hosts and vectors largely depend on their habitat requirements (Hartemink et al. 2015).".

4. L 21-22: Not sure what this means. "elaborated" is not a logical word in this sentence, but I'm not sure what the point is except to say simply that population dynamics vary across space and time but control strategies are typically carried out in a uniform fashion, "potentially impairing management". We rephrased to: "Spatial and temporal variations in environmental suitability could induce unexpected changes in the dynamics of the vector population. Despite this, insect pest management

strategies are often designed and implemented without considering local environmental specificities, potentially reducing the chances of success."

5. L 25: Should be "cause both" Corrected

6. The paper is generally well-written, though there are some vocabulary and grammatical errors typical of non-native English. I've only pointed out a few easy fixes or problems that impair understanding. The paper has been read by a native English speaker (M. Vreysen, one of the co-authors). We also corrected as proposed the errors highlighted.

7. L 41-46. I totally agree, and can't wait to quote this whole paragraph in a lecture. Thanks!

8. L 45: except, remove the word "easily". Done

9. L 47: should probably be "...entomologists have developed a number of models (refs), and encouraged…" Modified as proposed

10. L 51. "ineffective" would be a better word choice than "misleading" as there isn't likely to be such a nefarious or neglectful intent (which is what "misleading" implies)! Corrected

11. L 52: Not sure what "area-wide principles" are. Is this jargon? Area-wide principles imply that the full target population is considered at once. A reference has been added: Hendrichs, J., P. Kenmore, A. S. Robinson, and M. Vreysen. 2007. Area-Wide Integrated Pest Management (AW-IPM): Principles, Practice and Prospects, pp. 3-34. In M. Vreysen, A. S. Robinson and J. Hendrichs (eds.), Area-Wide Control of Insect Pests, From research to field implementation. Springer, Dordrecht, The Netherlands.

12. L 53: "imputed" should be "due"? Corrected

13. L56 - 65. There's a lot of repetitiveness and filler phrases here, plus some grammatical errors. I suggest: Remove "To address such an issue..." and simply write "Spatial complexity of the environment has been shown to considerably influence predictions (refs). Indeed, population dynamics are expected to vary locally among patches of variable suitability, possibly affecting population dynamics at the larger metapopulation scale. To assess whether spatial and temporal heterogeneity drives tsetse fly population dynamics at the metapopulation scale, we developed..." Corrected

14. L 69: "harbor" is a bit anthropomorphic. I suggest "tsetse flies are highly structured across the metapopulation" Corrected

15. The final paragraph of the introduction should also include the goal of assessing control methods (increasing adult mortality), as this forms the basis for the manuscript's most interesting result. Now included

16. L 76: should be "influential". Corrected

17. L 77-78: I suggest "However, it's influence compared to, or combined with, demograpihc processes [is poorly understood/has not been shown or explored]." Corrected

18. 80-81 & 86: Be more precise about the temperatures at/over which these things occur. The range of temperature is 20-30°c and is now indicated in the text.

19. At this point, the reader does not know what a "teneral" is. We replaced "teneral" by "nulliparous" and defined the term at its first use.

20. L 92: should be "models" and "in the savannah group". Corrected

21. 98: should be "associated with human [irrigation?] activities". Corrected

22. 100: "Hence..." Actually, it is not clear how this differs from previous models because it's not clear how savannah flies differ in behavior and distribution. Need more information. Indeed, the main difference does not come from the species being in the savannah group but more because the

metapopulation is in a fragmented landscape. Usually, riverine species disperse along rivers, thus in one dimension, while tsetse in the two other groups disperse in two dimensions. However, because of the patchy landscape, the species retained in the present paper also disperse in two dimensions, making it a good candidate for broader findings, not restricted to riverine species. This was not clear enough thus we revised the sentence to: "(…) and disperse in two dimensions like tsetse flies of the *fusca* and *morsitans* groups".

23. L 113: hold should be "held". Corrected

24. L 124: specify what the names are referring to: "was monitored in four areas: Hann, ...". Also, they are not labelled in Figure 1, but probably should be. Corrected and Fig. 1 now include the names of the areas.

25. L 145: temperature largely increases or decreases? The temperature increases from the centre of a gallery forest towards its edges. It is now clearly stated.

26. Figure 1 should be two separate figures. This would give more space to also label the four sites. Also, "30x30 [m? km? cell?] simulated area..." It is not clear what scale the maps are showing. There should also be more clear legends in all figures. Here, the color scale should be labelled as number of individuals. The Figure 1 has been revised. The part on the model is now in appendix as it is required to reproduce our work but not to understand the whole story. The revised version of the figure provides the location of the four sites, the resolution of the grid, and the label of the colour scale, as well as the life cycle of tsetse flies, which occurs within each cell.

27. L 155: "predict" from here on out, it is not clear what conditions are being used to project a prediction onto. A table with the starting conditions/parameter values and those used for the various "scenarios" is needed. A table with the parameter values was provided in Supporting Information, Table S2. It is now used much earlier in the text, and wherever it is helpful. The paragraph "model analysis" has been renamed "model setting and sensitivity analysis" and reorganised to make it clearer. Initial conditions are always the same (i.e. the conditions obtained after the 3-year burn-in period using reference parameter values). Except temperature, parameters and multiplying factors all varied from 95% and 105% of their reference values in the sensitivity analysis. In the control scenarios, only adult mortality varied (same initial conditions, all the other parameters to their reference values). During the new resurgence scenario, reference parameter values were used. Hence, no additional table was provided here, but the text was made clearer.

28. L 158: There really should be a section on fly development, and maybe also a life-cycle diagram to accompany the model in Figure 1. It's just really difficult to follow for a non-specialist without this basic knowledge. Also, what is a "parity"? Is this jargon or a translation error? The word does not appear in Hargrove & Ackley 2015. Perhaps the authors mean "stages"? If so, this should be fixed throughout. As stated in comment 26, the Figure 1 has been revised and now include a life cycle of tsetse flies instead of the model diagram which is in appendix (as this diagram is not required to understand the paper but is required to reproduce it). "Parity" was replaced by "ovarian age", which is defined by the number of pupae which have been produced (none for nulliparous N, one for F_1, etc.).

29. L 161: Please cite the reference for this. The associated reference is "Solano, P., J. Bouyer, J. Itard, and D. Cuisance. 2010. Cyclical vectors of trypanosomosis, pp. 155-183. In P.-C. Lefèvre, J. Blancou, R. Chermette and G. Uilenberg (eds.), Infectious and parasitic diseases of livestock, vol. 1. Éditions Lavoisier (Tec & Doc), Paris."

30. L 163: Should be "The model was implemented in Python..."? Corrected

31. Equations: given the mixed use of cases and super- and sub-scripting in these equations, I suggest a font that helps to distinguish them more clearly, if possible. We did our best to make equations as readable as possible. No superscripting was used except for exponential terms, which was thus replaced by '*exp*(…)' to avoid superscripting.

32. L 181-183. Why are Males not included in X (adults and tenerals) here? Males mate from the age of 6 days regardless of temperature. Then, they are only subject to mortality (Solano et al. 2010a). They were kept in the model because they play a role in density-dependent processes. Their development was kept as simple as possible.

33. L 191-192: What does this mean, both mathematically and biologically? We reformulated to "Individuals who reached state n_S (i.e. stage S is completed) evolved to the next stage. A pupa was produced at the end of both nulliparous and parous female stages. After the fourth ovarian age, parous females looped back to the start of F_{4+} (i.e. stage F_{4+} represented females who have produced at least 4 pupae)."

34. L 196: Ref should be Lloyd-Smith. Corrected

35. L 205: I am not familiar with this type of spatially-explicit model. It seems similar to a cellular automata model, but the authors do not call it that. In a cellular automata framework, the edges must be treated in a pre-determined way (reflective, hard, wrap-around), and that can affect the results. Perhaps this framework does not need this specified, but I am at least personally curious how the "neighborhoods" are treated at the edges of the grid. The number of neighbours of a given cell is function of the dispersal radius (r) and of its place in the grid. With a radius set to 1 cell, cells not on the edges have 9 neighbours (the cell itself and diagonals are included). On the edges (and corners), cells have fewer neighbours, and only those neighbours' attractivities are normalized into probabilities for the spatial distribution of dispersing flies. This choice means that flies in cells on the edges and corners have less destinations to choose from when moving.

36. L 207: very cool! Thanks!

37. L 212 & 218: again, the model scenario parameters should be in a table in the main text. The reader does not have a clear idea what these scenarios are because they have not been explicitly laid out. For sensitivity analyses, the authors could specify these ranges in the same table using brackets, etc. This would help the reader understand their methods and help with interpreting the results. To keep the paper as short as possible, we maintain Table S2 in Supplementary material, but we now use it much earlier. For the sensitivity analysis, all parameters and multiplying factors except temperature varied by ±5% of their reference value, as stated in the paragraph on sensitivity analysis. We reorganised the section to make it clearer (see comment 27).

38. L 215: "old" is a bit crude. "mature"? Changed to "females of ovarian age 4 and more".

39. L 216: fine to give this mathematical expression but it needs to be referred to (also) in words in the sentence. We now state: "predicted age structure was compared with field data for females of ovarian ages 1, 2, and 3: [formula]"

40. L 224: preserve model hypotheses? what does that mean? We rephrased: "to maintain a similar order of values"

41. L 224: Is the weighting coefficient already given in the equations? if so, reference it here. If not, it should be. This indeed was not clear. We rephrased it by: "Mortality and development functions of each life stage were varied using multiplying factors (i.e. function formulas were kept). The reference values of multiplying factors were all equal to one." These multiplying factors are not part of the equations. They are used to vary the values without varying the parameters of the functions, as this would have modified also the shape of the functions, which was not what we wanted to assess.

42. L 235 & 236: again, these expressions should be given names in words within the sentence. We rephrased: "We computed for each cell c after one year of control: (1) the proportion of females in the area which were located in that cell, $\frac{T_{t=1\ yr,c}}{\sum_i T_{t=1\ yr,i}}$, which indicated cells with the highest proportion of the female population; (2) the abundance of females in cell c in the control vs. pre-control scenarios after one year, $\frac{(T_{t=1\ yr,c})_{control}}{(T_{t=1\ yr,c})_{pre-control}}$, which quantified the local impact of increased mortality."

43. L 237-238: how was this assessed? This now concerns also resurgence. We rephrased it to: “We analysed the relationships between the local environmental variables (carrying capacity, mean temperature, temperature variance in each cell) and these three cell indicators, reflecting different properties of the population spatial structure.”

44. L 245: "female mortality" Corrected.

45. L 246: "followed a logistic [function/ distribution]" Corrected.

46. Figure 2: This figure is barely legible. I completely understand it can be difficult to show data from multiple sources, but better labelling could help. Two minor notes: dots --> "points" and the first panel should say "adult female daily mortality rate" instead of just daily mortality rate (right?). Also, in all figures, the A) B) C) panel labels should be outside of the figures and much larger. This figure has been revised following the suggestions of the reviewer. To keep space for new results (targeted increase in mortality and population resurgence), this figure has been removed from the main text and is now in appendix.

47. L 251-253. The presentation of these data are confusing here because the authors present them in terms of properties of the "cells" or "grid" rather than "sites" or "landscape" or something real-world. Instead, it sounds like they are reporting a set of parameters rather than results. The authors could present the findings, then simply say the cell and grid properties were defined according to these empirical conditions. We replaced the number of individuals per cell (250m x 250m) by the local fly density per km², and “grid” by “simulated landscape”.

48. L 256: "were seasonal" Corrected.

49. L 257: female population was stable? was it not also seasonal? perhaps "consistent" across years would be a better term? Where do we see these data? We now use “similar across years”. These results are shown Fig. 2B.

50. L 260: the figure does not (at least, clearly) capture this statement. Yes indeed, this statement is true but not shown in the figure, which is now said.

51. Figure 4: both panels need legends for the line types and colors. Also, delta X: should it not be "time to development" ? be consistent. Corrected (now Fig. 3)

52. L 270: How were interactions assessed? Is this result simply due to the low variance? We used a variance-based global sensitivity analysis (FAST) to assess how the variations in parameters impacted the variations in model outputs, all parameters varying simultaneously. For each varied parameter, this analysis provides two sensitivity indices: one for the principal effect (as if the parameter was varied alone), the second for the sum of interactions involving this parameter.

53. L 272: "to levels" Corrected.

54. L 278: I am not convinced by simply looking at these two figures. Too much going on in each to understand what the authors are pointing to. This section has been fully revised and reorganised, with new results being presented on applying an optimized targeted control (heterogeneous in space) and on population resurgence after control (in both situations of a homogeneous and heterogeneous control). Without increasing the number of figures, we particularly paid attention to the clarity of take-home message per section. We hope results are now easier to understand.

55. L 278-283: This whole section is really not clear. Revise. See previous answer.

56. Figure 5: I do not understand why/how the 60% increase in adult mortality in scenario 3 leads to complete loss of the entire female population in time step #1 for shorter-lived flies. How does it crash this fast (in a single time step)? On this figure, time was in years, thus for such a high adult mortality the population crashed in one year (not in a single time step). This figure is no longer in the paper, it has been replaced by a one-year control.

57. L 290-291: really? Could there simply not be enough power? The figure shows that the different levels of temperature variations were observed all over the mean temperature range, it is not a matter of statistical power but of the variety of situations encountered among the 900 cells. Despite small ranges (both for mean temperatures and temperature variations), the efficacy of a homogeneous control increased with these two criteria and not with carrying capacity. It also impacted resurgence (with lower growth rate for higher temperatures and variations) after a homogeneous control (new results). However, it was no longer true for a heterogeneous control (new results).

58. L 297: "can be" : has this been shown (in Vreysen et al 2011), or are the authors speculating? L 299: does Vreysen et al 2011 refer to this case in Zanzibar? If so, please clarify, and if not, please reference. Yes, in Vreysen et al. 2011, we demonstrated that sterile males were aggregated in the same sites as wild males when released by air, and it was a statistical re-analysis of the Zanzibar eradication campaign. The sentence was reformulated to make this clearer.

59: L 305-306: I completely agree, but have the authors sufficiently demonstrated this? It would be nice to see population dips then resurgences in population numbers over time. This I think is crucial. Thanks for the suggestion. In the first version of the manuscript, we thought that adding such information on population resurgence after control would render the paper message too complex. As suggested, we have looked at population dynamics during the year following a one-year control both with a homogeneous and a heterogeneous control. The ratio of the local population size after one year of control over its size if not controlled was a proxy for local control efficacy, which could be correlated to local landscape characteristics (e.g. carrying capacity, average temperature, temperature variations in the cell). The local population growth rate over the year after control localised cells with the highest local rates, highlighting possible refuges. Results are very interesting. Local temperature plays a role both on control efficacy and resurgence limitation in the case of a homogeneous control. Local temperature plays a minor role once control is spatially targeted (heterogeneous control), and the controlled population is much more dispersed. New figures have been added.

60. L 313-316: this sentence is a bit confusing, re-word? It has been changed to: “In addition, isolated populations could merge if close enough together in a changing habitat, possibly impairing control strategies. Conversely, new populations could become isolated, all the more as temperature is the first driver of landscape friction in tsetse (Bouyer et al. 2015).”

61. L 320-321: how are "realistic patterns" different from "knowledge-driven ones"?? The sentence was unclear. We rephrased: “The model used realistic assumptions and highlighted the importance of refuges in this species, which was not previously evidenced using theoretical assumptions (Childs 2011), knowledge-driven patterns (Barclay & Vreysen 2013), or aggregated patterns assuming a binary occupancy (Lin et al. 2015).”

62. L 330: "complementary" Corrected

63. L 333: This sounds like the authors tested control targeting reproduction, which was not the case (unless I've missed something) rather than referring to the sensitivity analysis. If so, the language should be a bit more careful, as sensitivity depends on the range and variance of the parameter values used and response variables chosen. This may be nit-picking, but perhaps using the term "sensitive" in the sentence could resolve the ambiguity. Rephrased to: “The fact that tsetse fly population dynamics was much more sensitive to mortality than reproduction is …”

64. L 334: "willing to avoid mortality at all costs" is way too anthropomorphized. Please rephrase to better explain the phenomenon or cost in a biologically-meaningful way. Rephrased to: “In this species, individual survival is prioritized over breeding”

65. L 340-347: It's not clear what point this paragraph is meant to make. Also, "species' ecological strategy" We agree that this paragraph was quite useless in the previous version of the manuscript. Now that we have completed the story with targeted control and population resurgence after control, a general paragraph on relevant control options according to species characteristics appeared useful,

before discussing control options specific to tsetse (following paragraph). Hence, this paragraph was kept.

66. L 378-379: This sentence starts out clear, then falls apart. Maybe revise and break into two after "disappear"? The conclusion has been revised. We hope it is clearer. We also included the new results: “To conclude, environmental carrying capacity largely explained the contribution of local source spots to tsetse fly population dynamics at a large scale, but unfavourable conditions result in a progressive disappearance of such spots and the existence of refuges that located in colder areas where the temperature is less variable. When applying a spatially homogeneous increase in adult mortality for one year, population size was less impacted in such refuges. In contrast, applying a spatially heterogeneous increase in adult mortality resulted in refuges located at the interface between controlled and uncontrolled zones, and previous temperature-dependent refuges disappeared. Areas to be controlled should be chosen with caution when facing a heterogeneous habitat. Our study confirmed the importance of a preliminary characterization of the study area before the start of control operations in order to include the most suitable habitats in the control strategy, which is the foundation of area-wide integrated pest management.”.