Optimising passive surveillance of a neglected tropical disease in the era of elimination: A modelling study

Short title: Passive surveillance design in an elimination setting

Joshua Longbottom (MRes) [1, 2], Charles Wamboga (MD) [3], Paul R. Bessell (PhD) [4], Steve J. Torr (PhD) [1], Michelle C. Stanton (PhD) [1, 2]

Author Affiliations:

[1]Department of Vector Biology, Liverpool School of Tropical Medicine, Liverpool, L3 5QA

[2]Centre for Health Informatics, Computing and Statistics, Lancaster Medical School, Lancaster University, Lancaster, LA1 4YW

[3]Ministry of Health, Kampala, Uganda

[4]Epi Interventions, Edinburgh, UK

Corresponding Author:

Mr Joshua Longbottom, Department of Vector Biology, Liverpool School of Tropical Medicine, Liverpool, L3 5QA

Joshua.Longbottom@lstmed.ac.uk

Abstract

Background: Surveillance is an essential component of global programs to eliminate infectious diseases, with surveillance systems often being considered the first line in averting epidemics for (re-)emerging diseases. As the numbers of cases decline, costs of treatment and control diminish, but those for surveillance remain high even after the 'last' case. Economies made by reducing surveillance risk missing persistent or (re-)emerging foci of disease, therefore it is vital that surveillance networks are adequately designed; however, guidance on how best to optimise disease surveillance in an elimination setting is lacking. Here, we use a simulation-based approach to determine the minimal number of passive surveillance sites required to ensure maximum coverage of the population at-risk (PAR) of an infectious disease.

Methodology and Principal Findings: For this study, we use Gambian human African trypanosomiasis (g-HAT) in north-western Uganda, a neglected tropical disease (NTD) which has been reduced to historically low levels (<1000 cases/year), as an example application. To quantify travel time to diagnostic facilities, a proxy for surveillance coverage, we produced a high spatial-resolution friction surface and performed cost-distance analyses. We simulated travel time for

the PAR with different numbers (n = 1...170) and locations (170,000 total placement combinations) of diagnostic facilities, quantifying the percentage of the PAR within 1h and 5h travel of the facilities, as per in-country targets. Our simulations indicate that a minimum of 54 diagnostic centres are required to meet provisional targets, and we determine where best to place these facilities, enabling a minimal impact scale back from 170 facilities operational in 2017. Scaling back operational facilities ensures that costs can be reduced without impairing surveillance of the core areas with remaining cases.

Conclusions: Our results highlight that surveillance of g-HAT in north-western Uganda can be scaled back without reducing coverage of the PAR. The methodology described can contribute to cost-effective strategies for the surveillance of NTDs and other infectious diseases approaching elimination or applied to (re-)emerging diseases for which the design of a novel surveillance network is required.

Author Summary

Disease surveillance systems are an essential component of public health practice and are often considered the first line in averting epidemics for (re-)emerging diseases. Regular evaluation of surveillance systems ensures that they remain operating at maximum efficiency; systems that survey diseases of low incidence, such as those within elimination settings, should be simplified to reduce the reporting burden. A lack of guidance on how best to optimise disease surveillance in an elimination setting may result in added expense, and/or the underreporting of disease. Here, we propose a framework methodology to determine systematically the optimal number and placement of surveillance sites for the surveillance of infectious diseases approaching elimination. By utilising estimates of geographic accessibility, through the construction of a friction surface and a simulation approach, we identify that the number of operational diagnostic facilities for Gambian human African trypanosomiasis in north-western Uganda can be reduced without affecting coverage targets. Our analysis can be used to inform the number and positioning of surveillance sites for diseases within an elimination setting. Passive surveillance becomes increasingly important as cases decline and active surveillance becomes less cost-effective; methods to evaluate how best to engage this passive surveillance capacity given facility capacity and geographic distribution are pertinent for several NTDs where diagnosis is complex. Not only is this a complicated research area for diseases approaching elimination, a well-designed surveillance system is essential for the detection of emerging diseases, with this work being topical in a climate where emerging pathogens are becoming more commonplace.

Introduction

Quantifying the spatial and temporal distribution of cases is essential for the development, implementation and monitoring of programmes to control or eliminate infectious diseases (1-3). In general, costs for treatment and control of a disease scale with the number of cases, but those for surveillance can be high even when disease incidence is low (4). Programmes aiming to eliminate or eradicate a disease maintain high levels of surveillance, as illustrated by the global programmes against smallpox and polio (5, 6). Similarly, surveillance systems to detect (re-)emerging diseases may also have relatively large surveillance costs in relation to the numbers of cases (7). Maintaining adequate surveillance for diseases approaching elimination or with potential for emergence can be prohibitively costly for national health systems, particularly for resource-poor countries in the tropics (8, 9), and as such, approaches for cost-effective surveillance are required.

Neglected tropical diseases (NTDs) cause high levels of mortality and morbidity in some of the world's poorest countries (10, 11). A global program aims to eliminate or eradicate eleven NTDs by 2030 and as the elimination of several NTDs approaches, globally and/or nationally, there is a pressing need for cost-effective strategies to detect the last remaining cases (12, 13). The new surveillance strategies will need to be adapted to the disease itself, local health systems and the population at risk (PAR) (1).

Disease surveillance systems include active, passive, sentinel, and statistical approaches, but the majority of reportable disease surveillance is conducted through passive surveillance (14, 15). Passive surveillance is based primarily on compilation of case reports submitted by healthcare facilities, produced when infected individuals present to the facility for diagnosis and treatment. One approach to improving cost-effectiveness of passive surveillance is to quantify the minimal number of surveillance sites that provides maximal coverage of the PAR. Towards this aim, we combined estimates of travel time to passive surveillance sites with a simulation-based approach to determine the minimal number of sites required to ensure that 50% and 95% of a PAR of Gambian human African trypanosomiasis (g-HAT) are within 1-hour and 5-hours of a diagnostic facility, respectively. The approach described here can be adapted for a range of NTDs in an elimination setting.

Scale back in the context of human African trypanosomiasis

Human African trypanosomiasis (HAT, also called 'sleeping sickness') is an NTD occurring across sub-Saharan Africa, caused by sub-species of *Trypanosoma brucei* transmitted by tsetse flies. Most (>95%) cases of HAT are caused by *T. b. gambiense* (g-HAT), for which humans are the primary host; the remaining ~5% of cases are caused by *T. b. rhodesiense*

(r-HAT) for which the primary reservoir is animal hosts (16). No prophylaxis or vaccine exists for either form of HAT. Therapeutic drugs are available (17), but the toxic nature of chemotherapy requires that infection status is confirmed before the patient is treated. Disease prevention and control efforts focus on the detection and treatment of existing cases and control of the tsetse vector (18).

The World Health Organization (WHO) aims to eliminate g-HAT as a public health problem by 2020. The definitions of elimination include fewer than 2,000 cases reported per annum globally, a 90% reduction in areas reporting >1 case in 10,000 per annum compared to 2000–2004, with a country-level indicator of elimination defined as fewer than 1 reported case per 10,000 people, per annum (averaged over a 5-year period) in all health districts, in conjunction with adequate, functional control and surveillance (19). Uganda is on track to achieve this goal with a reduction from 2,757 (range, 310-948 cases/year) cases reported between 2000-2004 to 18 (range, 0-9 cases/year) cases in 20014-18 (20). These reductions are mostly attributable to active screening and treatment of the population (21, 22), and, more recently, vector control (23). For g-HAT, active screening has been the cornerstone of surveillance in most foci during periods of high case numbers. As case numbers decline this has become increasingly less cost-effective and surveillance has switched to a passive system. In 2013, a new passive surveillance strategy was implemented which saw the number of facilities participating in passive surveillance increase from four to 212 and subsequently adjusted to 170. The majority of facilities conduct only serological surveillance using a rapid diagnostic test (RDT) and 12 accept referrals of RDT positive patients for confirmation by microscopy (24).

Plans to scale back the number of passive surveillance sites operating RDTs are ongoing in Uganda, with the target of ensuring that by 2030, >50% of at-risk populations should live within 1-hour of a health facility with HAT diagnostics and >95% should live within 5-hours (25). The number of health facilities using HAT RDTs were reviewed in July 2014 and September 2015, in response to the evolving epidemiological situation of g-HAT in Uganda (24). Previous analyses utilised the Euclidean distance to facilities as opposed to estimates of travel time. The number of facilities in operation may be further reviewed to better quantify accessibility, identify the minimal number required to ensure sufficient coverage, and to maximise cost-effectiveness.

Optimisation of passive screening capacity in NW Uganda must consider two key elements; firstly, there must be evidence of reduced transmission, be this supported by active screening or reduced abundance of tsetse (22, 23); secondly, g-HAT has a very long interval between infection and detection of a case, and cases can remain undetected for

some time (26), therefore we are required to consider the long tail of this case distribution and any reservoirs of infection (27). Consequently, the resource review proposed here should target a wider area that has been historically at risk in order to detect any residual infections in the area. The streamlining or optimisation of the number of facilities might be considered a step towards establishment of a network of sentinel screening sites to monitor post-elimination (16).

The work described here aims to utilise information on the location of operational HAT diagnostic facilities, alongside estimates of travel time to said facilities, to inform an analysis designed to identify the minimal number of surveillance facilities required to meet the in-country coverage targets defined above.

Methods

Study setting

The focal area of this study is north-western Uganda where we focus on seven districts within the West Nile region which form Uganda's g-HAT endemic area. These endemic districts are Arua (2,100 km^2), Maracha (693 km^2), Koboko (862 km^2), Amuru (3,625km^2), Adjumani (3,030km^2), Moyo (1,800km^2), and Yumbe (1,524 km^2). Collectively, these districts have a population of approximately 3.5 million people (28). For the purpose of this study, from this point onwards, we refer to these seven districts as "north-western Uganda".

High-resolution resistance surface

To quantify travel time to diagnostic facilities, we first sought to generate a resistance surface for north-western Uganda at a 30m × 30m spatial resolution. Resistance surfaces (also termed 'friction surfaces') contain estimates of associated travel cost for gridded cells within a Cartesian plane and are used within cost-distance analyses to quantify the effort required to travel between each cell and an origin point (29). To construct the resistance surface, we collated data from a variety of sources. We obtained comprehensive road network data from OpenStreetMap (30), and assigned travel speeds along differing road classes based off observed speeds from GPS tracks obtained during February-April 2018 (31). Speeds were representative of motorcycle travel, in agreement with the most commonly used mode of transportation in Uganda (32). Estimates of off-road travel were generated utilising remotely sensed Landsat-8 data (33), and a normalised difference vegetation index (NDVI) (34, 35), paired with information from studies detailing travel time through varying vegetation densities (36, 37). Finally, we combined off-road and on-road travel estimates to produce a comprehensive resistance surface detailing the time taken to traverse through each 30m × 30m gridded cell. We evaluated the accuracy

of the resistance surface by comparing predicted travel time along 1,000 routes with times derived from Google Maps within a linear regression (38). An in-depth description of the process is provided within Supplementary File 1.

Health facility data

During 2017, there were 170 HAT diagnostic centres in operation within north-western Uganda (24). Each facility utilises either RDTs alone (39), or RDTs and microscopy techniques (40), and supplemented by mini-anion exchange centrifugation technique (mAECT) (41), with three of these second group facilities also equipped with loop-mediated isothermal amplification (LAMP) for identifying suspected g-HAT cases (Fig. 1:A) (42). For facilities with available data, the number of RDTs used during 2017 is shown within Fig. 1:B. Facilities operating LAMP and LED diagnostics serve as referral sites for RDT positive individuals, and are representative of larger facilities with higher quality services (24).

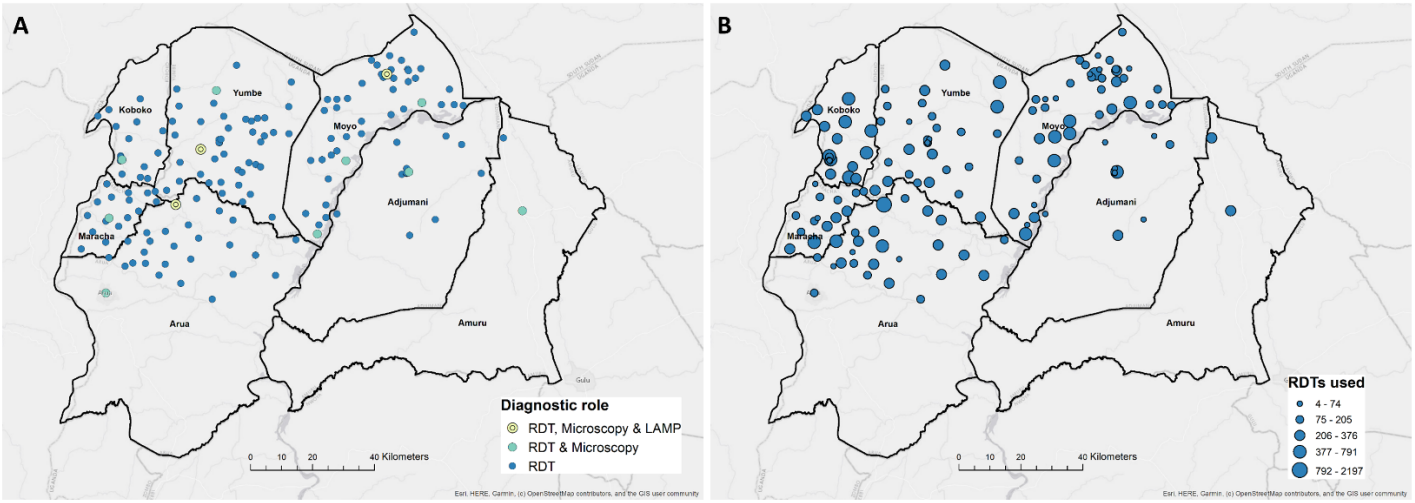

Figure 1. A: Location of existing HAT diagnostic centres across endemic districts in north-western Uganda (2017), coloured by type of diagnostic method used. B: Number of HAT rapid diagnostic tests (RDTs) used by facilities during 2017.

Human population density data

To detail the number of individuals within HAT risk areas who live within 1-hour and 5-hours travel time of a HAT diagnostic facility, we utilised a high-resolution population density surface (28). This surface matched the spatial resolution of the resistance surface generated above (30m × 30m) and was re-sampled to ensure gridded cells aligned. A crude estimate of the PAR of g-HAT within the study region was determined by creating a 10km radius buffer around

reported cases between 2000 and 2018 (Fig. 2:A) (20, 24), representative of moderate risk (Fig. 2:B). This identified 3,025,801 individuals living within at-risk areas.

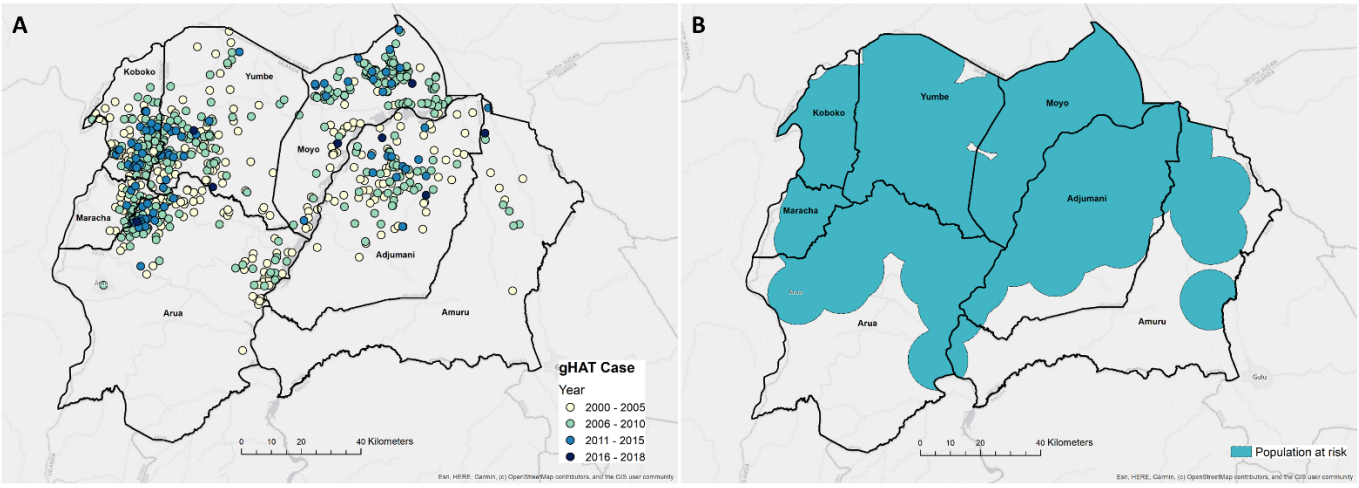

Figure 2. A: Spatial distribution of g-HAT cases within north-western Uganda, 2000-2018. B: Areas at risk of g-HAT, stratified as locations within 5km (severe) or 10km (moderate) of a case.

Simulation of accessibility to diagnostic centres under differing placements

Deriving the minimal number of facilities

To derive the minimal number of facilities required within north-western Uganda to ensure that more than 50% of the PAR live less than 1 hour, and 95% of the PAR live less than 5 hours from a health facility with HAT diagnostics respectively, we performed a simulation study. Suppose S_n is the set of all possible combinations of n facilities from the 170 currently available. We wish to obtain an estimate of the average PAR living within 1 or 5 hours of a facility for all possible values of n, however once $n > 1$, the total number of combinations of n facilities is very large and computationally prohibitive. As such, we adopted a simulation approach, such that for $n = 2,..,170$ we generated $\hat{S}_n$ which consisted of 1,000 random samples of n facilities. For each sample, $i = 1,...,1000$ we calculated the size of the PAR within 1, (A_n^i) or 5, (B_n^i) hours of any of the n facilities using a cost-distance analysis implemented within R (version 3.5.1). From this we can obtain M_n, the average number of people within 1 hour, and V_n, the average number of people within 5 hours of any of the n facilities (eqns. 1&2). Q_n represents the proportion of simulations for which more than 50% of the PAR, (D), are within 1 hours travel to any of the n facilities (eqn. 3), and Z_n represents the proportion of simulations for which more than 95% of the PAR are within 5 hours travel to any of the n facilities (eqn. 4). To avoid

spatial clustering within samples, we utilised an inhibitory sampling approach when generating $\hat{S}_n$, ensuring a minimum distance of 4km between sampled facilities (43). The minimal facility number simulation is outlined in eqns. 1-4:

$$M_n = \sum_{i=1}^{1000} \frac{A_n^i}{1000}$$

(Eqn. 1)

$$V_n = \sum_{i=1}^{1000} \frac{B_n^i}{1000}$$

(Eqn. 2)

$$Q_n = \frac{\sum I(A_n^i > \frac{1}{2}D)}{1000}$$

(Eqn. 3)

$$Z_n = \frac{\sum I(B_n^i > 0.95D)}{1000}$$

(Eqn. 4)

The minimal number of facilities, N^{min}, was identified when there was a negligible change in the proportion of PAR within 5-hours travel time of a facility, as defined by $Z_n - Z_{n-1} < 0.01$.

Deriving the optimal selection of facilities

Utilising the minimal number of facilities, N^{min}, identified from the simulation above, we ran further simulations to determine the optimal selection of these facilities to ensure the maximal coverage of PAR. It should be noted that the number of available combinations ($C(170, N^{min})$) is computationally prohibitive, therefore we employed a simulation approach utilising 10,000 random combinations of N^{min} facilities. For each sample, the total population within 1-hour and 5-hour of a facility was determined utilising a cost-distance analysis ($A_{N_{min}}^j$ and $B_{N_{min}}^j$ respectively, $j = 1, ..., 10000$). For these simulations, we did not employ an inhibitory sampling approach, with no minimal distance enforced between selected facilities within each sample. The optimal selection of the N_{min} facilities was the combination that resulted in the largest number of the PAR being within the pre-defined criteria.

As a baseline for which to assess the impact of a scale back on accessibility of the PAR, we generated a cost-distance surface including all 170 facilities, representative of the situation in 2017. We then compared the predicted travel time for each 30 × 30m cell under the optimal scale back scenario, with the predicted travel time under the scenario representative of 2017, to determine which geographic locations would be most affected.

Results

High-resolution resistance surface

The high-resolution resistance surface generated showed good agreement when compared with freely obtained estimates of travel time from Google Maps, for 1,000 randomly generated validation routes across north-western Uganda ($R^2 = 0.902,\ p < 2e^{-16}$) (Fig. 3:A). The spatial distribution of the origin and destination locations used within the validation process is shown as Fig. 3:B. Whilst there is strong correlation, modelled travel time does slightly under-estimate compared to Google (root-mean-square error = 14.98), this is likely due to our estimates relating to motorbike based travel, *vs* Google times being representative of car travel. Nonetheless, this validation process provided confidence in the resistance surface, and subsequently in our estimates of travel time to diagnostic facilities. To facilitate reproducibility and additional research applications within the region, the resulting resistance surface is provided as Supplementary File: 2.

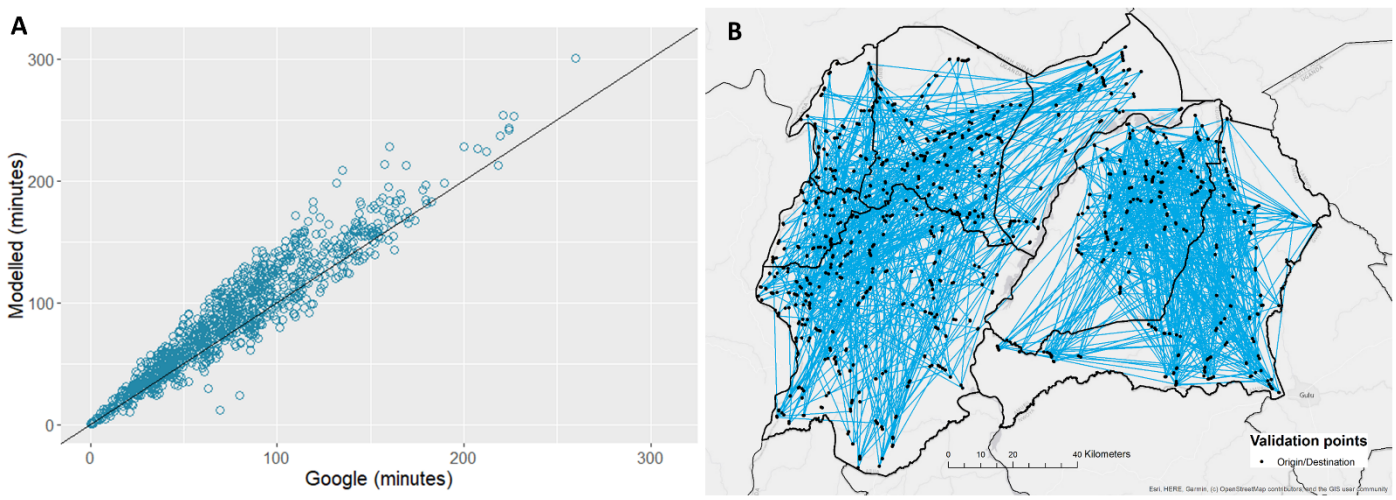

Figure 3. A: Result of a linear regression comparing observed travel times from Google Maps, and modelled travel time (our surface) ($R^2 = 0.902,\ p < 2e^{-16}$). B: Spatial distribution of origin/destination locations (black dots) used to validate the resistance surface. Blue lines represent pairing of origin/destination locations used to inform the regression presented in A.

Deriving the minimal number of facilities

Results from the simulation experiment defined in Eq. 1-4 indicate that a minimum of 16 facilities are required to ensure that 50% of the PAR live within 1-hours travel of a HAT diagnostic facility, and a minimum of 54 facilities are required to ensure and 95% of the PAR live within 5-hours travel (Fig. 4). These results highlight that the number of facilities operational in 2017 can be scaled back from 170 to 54 without losing significant coverage of the PAR.

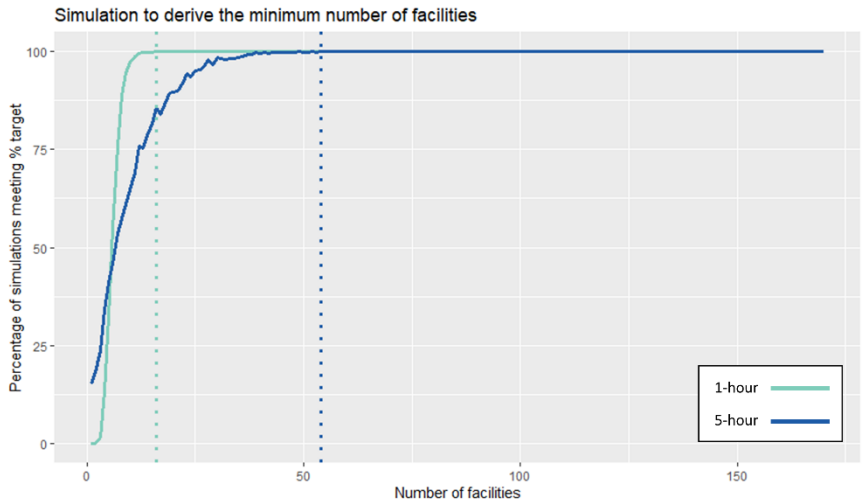

Figure 4. Results from the simulation to derive the minimal number of facilities required to ensure 50% of the population live within 1-hour travel time of a facility with HAT diagnostics (green) and 95% of the population live within 5-hours travel time of a facility with HAT diagnostics (blue).

Deriving the optimal selection of facilities

As a baseline for which to assess the impact of a scale back on the accessibility of the PAR, we first generated estimates of accessibility to all 170 facilities which were operational in 2017 (Fig. 5:A-B). The results from the cost-distance analysis utilising all 170 facilities indicate that 96.15% and 99.77% of the population at risk of HAT live within 1-hour and 5-hours travel time of a HAT diagnostic facility in 2017 respectively. We generated 10,000 estimates of travel time to facilities under varying selection combinations of 54 facilities and evaluated the percentage of individuals living within each coverage category. The optimal placement resulted in no significant difference in the proportion of the PAR living within 1-hours travel of a facility, when compared to the estimate utilising all 170 facilities (Chi-squared test, $P = 0.91$; all 170 facilities = 96.15%, 54 facilities = 95.12% coverage).

A comparison showing the accessibility to diagnostics is given in Fig. 5, detailing accessibility to all 170 facilities in operation during 2017 (Fig. 5:A-B) and the proposed scaled back, optimal placement of 54 facilities (Fig. 5:C-D). To aid interpretation, we visualise the cost-distance surfaces on a continuous scale (Fig. 5:A and Fig. 5:C), and on a categorical scale, with travel time binned by 30 minute increments (Fig. 5:B and Fig. 5:D). The difference in travel time from each 30m x 30m gridded cell, between all 170 facilities and 54 facilities is given in Fig. 5:E. A map detailing the optimal placement of the scaled back facilities is provided as Fig. 5:F, and a table listing the name, district and parish of facilities to preserve is provided (Supplementary File 1: Table S2).

Areas of greatest travel time to a facility include those locations which have a low population density, such as Maaji Parish in South-West Adjumani; Acwa Lolim Gr Parish, South-West Amuru and Pamujo Parish in Moyo. Additionally, large areas of Southern Arua have populations living within 1-hour + of a diagnostic facility, however, these populations are not generally considered to be living within areas of g-HAT risk.

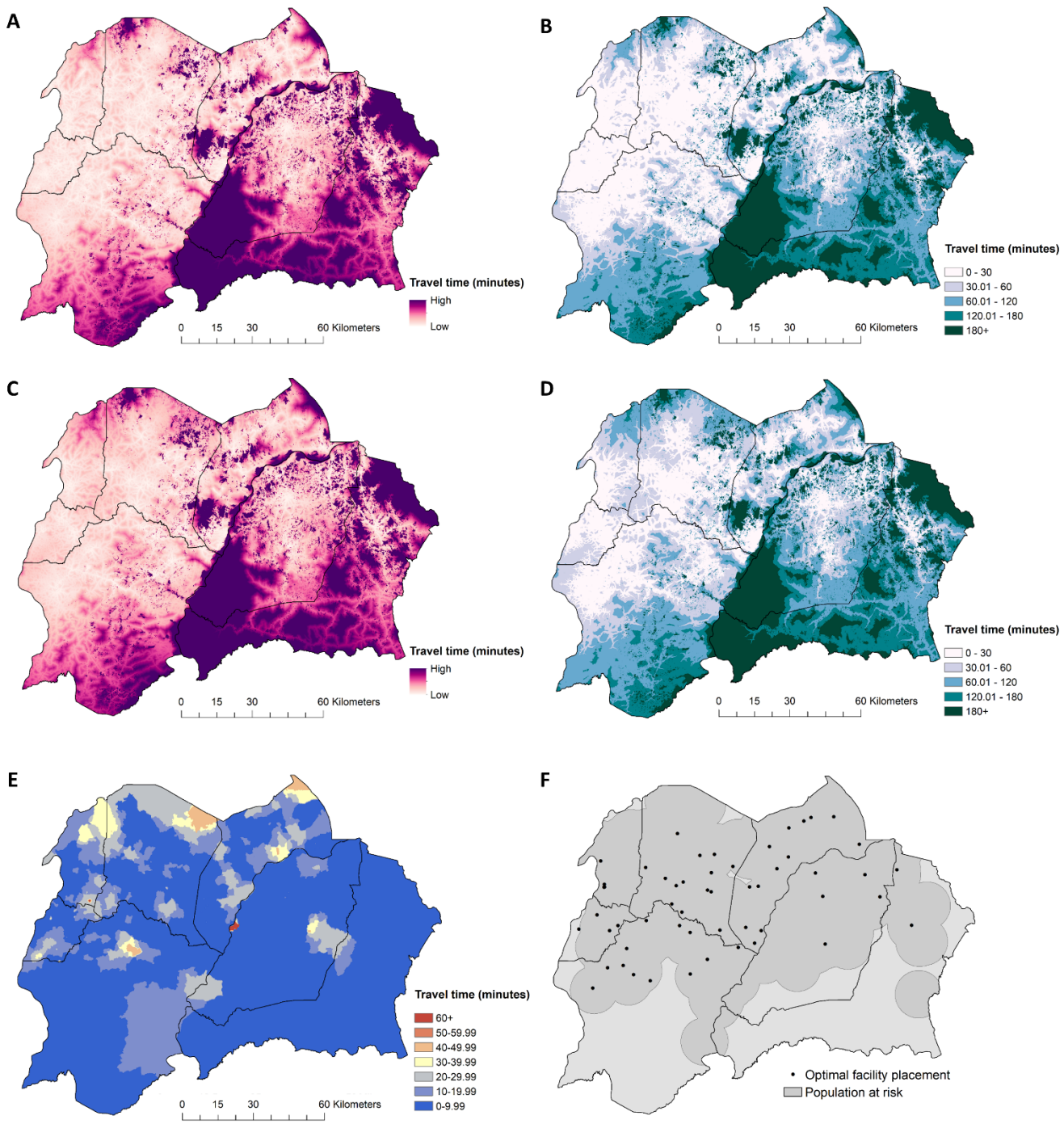

Figure 5. Predicted travel time, in minutes, to a g-HAT diagnostic facility. A) Predicted travel time (in minutes) to reach a diagnostic facility within the north-western Uganda, assuming the current, comprehensive distribution of 170 facilities. B) The predicted travel time surface detailed in A, presented as a categorical surface. C) Predicted travel time (in minutes) to reach a diagnostic facility within the north-western Uganda, using the optimal number and placement of facilities, as derived from the simulation study (n = 54). D) The predicted travel time surface detailed in C, presented as a categorical surface. E) The difference in travel time, for each gridded cell, between surfaces A and C. Red cells indicate

geographic areas where the increase predicted travel time, in the event of scale back, is greatest. F) The location of the optimal placement for the 54 facilities.

Discussion

Twenty years of a global programme for active screening and treatment of g-HAT has driven the global incidence to a historic low (16). Building on this achievement, recent advances in methods for detecting and treating g-HAT (17, 42), combined with more cost-effective methods of tsetse control (23), are providing the platform for achieving the WHO goals of eliminating g-HAT as a public health problem by 2020 and interrupting transmission completely by 2030. There will be a need for technical guidance on how to monitor the distribution and incidence of g-HAT in this elimination setting. Establishing cost-effective surveillance systems that can be maintained over the next decade will be crucial for the achievement of these ambitious goals.

Using a resistance surface informed by motorbike based travel, and a simulation-based analysis, we determined that the number of operational g-HAT diagnostic facilities within the north-western Uganda can be reduced from 170 to 54 (Fig. 4), whilst still ensuring that a large percentage of the PAR are within 1-hour and 5-hours travel (95.12% and 99.77% respectively) (Fig. 5). Through the scale back of the number of facilities, we can ensure maximum cost-effectiveness whilst still serving the entirety of the PAR. These simulations can be easily repeated as the spatial distribution of the PAR changes over time, through substitution of new surfaces detailing contracting or expanding PAR in response to case detection. This will allow a dynamic and rapid response to changing circumstances. Of note is that the PAR used in this analysis captures the historic distribution of g-HAT within north-western Uganda and is therefore greater than PAR surfaces generated using only contemporary data (i.e. Simarro *et al*. (44)), thereby providing higher confidence in the detection of disease and residual cases from across the area where transmission has occurred previously. This methodology, although applied to the surveillance of HAT, can also be adapted for a range of elimination scenarios and can also be utilised for the monitoring of emerging diseases as part of national early-warning systems.

Accessibility to a healthcare facility does not correlate precisely with Euclidean distance (45). The use of a validated resistance surface accounts for varying land cover and road network accessibility, factors ultimately affecting travel time, especially for remote and rural communities. By producing our resistance surface at a high spatial resolution, we also provide a more accurate quantification of travel time to a facility than existing surfaces at coarser granularity (46), giving higher precision when quantifying populations within each travel time category. Whilst the time taken to access a facility

313 likely influences an individual's decision to seek treatment, additional factors are also at play. Future efforts should
314 investigate the use of spatial interaction models to quantify the influence of other metrics on the probability of treatment
315 seeking at a specific location, i.e. gravity models weighted by staff capacity and their levels of training, status of the
316 laboratory and available materials for instance (47, 48). The construction and validation of such models requires
317 empirical measurements of treatment-seeking behaviour (49).
318
319 Although the travel time targets utilised within this analysis were pre-defined (25), further analysis is required to
320 determine the effects of these targets on treatment seeking behaviours. For instance, the cost of continuous travel to a
321 facility which is 1-hour or more from an individual's residence may present significant barriers to treatment (32).
322 Reducing the number of accessible facilities may also influence factors such as post-treatment follow up compliance,
323 with a previous study identifying costs for transportation to a facility as a reason for non-completion of treatment (50).
324 Alongside any adopted scale-back approaches, there is a need for sensitisation and information campaigns to inform the
325 PAR of the reduced availability of diagnostics as this information may influence treatment seeking behaviours (51); this
326 campaign can be used alongside a referral system to address such issues.
327
328 Scale back of disease surveillance should be integrated within a national development plan and combined with the scale
329 back of intervention programmes. In the context of Uganda, work is ongoing to investigate the effect of reducing the
330 geographical extent of tsetse control operations to areas where g-HAT persists. As disease prevalence changes within a
331 geographic area, approaches are required to ensure that appropriate surveillance and treatment systems are in place; the
332 method described here aims to ensure maximal coverage of surveillance under the most cost-effective scenarios. For
333 national programmes to adopt an optimised approach and integrate this approach within health care delivery systems, it is
334 important to demonstrate that the PAR remains adequately covered, health facilities are accessible, and that a functional
335 referral system is maintained. It is worth also noting that having strategic health facilities with a full range of tests for
336 disease confirmation is critical for elimination.
337
338 For other NTDs, plans to scale back surveillance require careful consideration of the country and disease in question,
339 alongside additional context-specific factors (1). As such, the altering of disease surveillance systems should be an
340 iterative process requiring regular reassessment of objectives and methods (9). The approach described here provides a
341 robust, reproducible framework to ensure maximal coverage of the PAR through the minimal number of sites within a
342 passive disease surveillance system.

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Author contributions

All authors conceived and planned the study. JL wrote the computer code and designed and did the analyses with input from PRB and MCS. Data was curated by JL, CW and PRB. SJT and MCS provided intellectual input into aspects of this study. All authors contributed to the interpretation of the results. JL wrote the first draft of the manuscript and all authors contributed to subsequent revisions.

Declaration of interests

We declare no competing interests.

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