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Data-driven models to predict the elimination of sleeping sickness in former Equateur province of DRC

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ABSTRACT

Approaching disease elimination, it is crucial to be able to assess progress towards key objectives using quantitative tools. For Gambian human African trypanosomiasis (HAT), the ultimate goal is to stop transmission by 2030, while intermediary targets include elimination as a public health problem – defined as <1 new case per 10,000 inhabitants in 90% of foci, and <2000 reported cases by 2020. Using two independent mathematical models, this study assessed the achievability of these goals in the former Equateur province of the Democratic Republic of Congo, which historically had endemic levels of disease.

The two deterministic models used different assumptions on disease progression, risk of infection and non-participation in screening, reflecting biological uncertainty. To validate the models a censor-fit-uncensor procedure was used to fit to health-zone level data from 2000 to 2012; initially the last six years were censored, then three and the final step utilised all data. The different model projections were used to evaluate the expected transmission and reporting for each health zone within each province under six intervention strategies using currently available tools.

In 2012 there were 197 reported HAT cases in former Equateur reduced from 6828 in 2000, however this reflects lower active testing for HAT (1.3% of the population compared to 7.2%). Modelling results indicate that there are likely to be <300 reported cases in former Equateur in 2020 if screening continues at the mean level for 2000–2012 (6.2%), and <120 cases if vector control is introduced. Some health zones may fail to achieve <1 new case per 10,000 by 2020 without vector control, although most appear on track for this target using medical interventions alone. The full elimination goal will be harder to reach; between 39 and 54% of health zones analysed may have to improve their current medical-only strategy to stop transmission completely by 2030.

1. Introduction

Gambian human African trypanosomiasis (HAT), also known as sleeping sickness, is a tsetse-borne disease caused by the parasite *Trypanosoma brucei gambiense*. The World Health Organization (WHO) has laid out two targets towards the elimination of Gambian HAT. The first target, to be achieved by 2020, is defined by two indicators (i) to eliminate HAT as a public health problem, defined as less than one reported case per 10,000 people, in 90% of HAT foci and (ii) reduce annual reported cases globally to <2000 (Holmes, 2014). The second target for this disease is to terminate transmission by 2030 (Holmes, 2014).

The natural history of Gambian HAT is slow, and consists of two distinct stages (1 and 2). During stage 1, which typically lasts

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around 17 months (Checchi et al., 2008), infected individuals initially experience mild or no symptoms that can easily be mistaken with malarial infection (Lejon et al., 2013). Stage 2 marks the transition of the parasite across the blood-brain barrier and the onset of severe disease with symptoms including behavioural disturbances, lethargy and usually death without treatment (Kennedy, 2013).

Despite an estimated 57 million people living at risk of Gambian HAT infection, the global trend of declining cases and lowered risk levels is promising and appears on track to meet the WHO's milestones by 2020 (Simarro et al., 2012). The decrease was mainly achieved through widespread detection and treatment interventions. Detection may be either "passive", when symptomatic individuals self-present at health facilities, or "active", when mobile teams screen at-risk villages. The recent development of cost-effective methods of tsetse control offer the prospect of adding vector control to case detection and treatment. Tsetse control through tiny targets is one such method and has been effective in regions including HAT foci in Guinea (Courtin et al., 2015), Uganda (Tirados et al., 2015) and Chad (Mahamat et al., 2017). Tsetse interventions have also been implemented recently in the Yasa-Bonga health zone (an administrative unit of former Bandundu province) of Democratic Republic of Congo (DRC), but not within former Equateur province.

A combination of active-screening programmes and declines in vector populations through the growth of human populations have shrunk many of the historic foci of HAT across West Africa, such that 87% of the Gambian HAT burden was estimated in 2014 to occur in DRC (WHO, 2015). Within DRC there are also high levels of geographic heterogeneity in disease burden. Of the former eleven provinces that existed pre-2015, Equateur province in the northwest of DRC had the highest number of reported HAT cases, 6828, in the year 2000 and the third highest proportion of cases (17% of the total) between 2000 and 2012 (Lumbala et al., 2015).

Mathematical modelling provides a method with which to assess quantitatively progress towards the WHO goals and project forwards to 2020 and 2030 (Hollingsworth et al., 2015). This type of mechanistic modelling has predictive power to test a range of plausible scenarios, enabling not only analysis of current interventions but also to predict the likely impact of current and alternative intervention strategies in the future. In this study, human case data from the former Equateur province was used to fit and validate the models (Model W and Model Y) of two independent research teams before generating predictions for the future of HAT in this region (see Methods and SI1 for model details).

Despite many of the mechanisms of transmission being known, some features of the epidemiology are less well understood; much of the key epidemiology that impacts on model assumptions is discussed elsewhere (Rock et al., 2015a). There is some evidence that some infected individuals may not follow the standard stage 1–2 progression; recently, evidence of parasitic infections in the skin (Capewell et al., 2016; Caljon et al., 2016) has highlighted some of the uncertainty that surrounds our knowledge of HAT infection and transmission to tsetse. Consequently, Model Y takes an assumption that some infected individuals will never develop symptomatic disease, and self-cure before progression to stage 2 infection. Other factors, which could impact transmission, include human behaviour that influences the tsetse biting rate on humans, with some individuals entering tsetse habitat more often and therefore having higher more bites, and hence infection. Model W has heterogeneous exposure of the population to tsetse bites to account for this. Other differences between the models included the infectivity of stage 2 patients towards tsetse and the susceptibility of non-teneral (previously fed) flies to infection (see SI1 for more details of all model assumptions).

By using multiple models, which have different underlying assumptions, the impact of these assumptions on forward predictions can be observed. Where results between the modelling teams are aligned, there is greater confidence in the model predictions, even if there is biological uncertainty in transmission. If there are conflicting results, it indicates that different biological hypothesis translate into different outcomes, and better more information may be required to improve certainty in predictions.

Both teams identify health zones in former Equateur province that may need revised strategies in order to achieve elimination as a public health problem by 2020, or full elimination by 2030. To inform policy planning and disease control, the groups also provide estimates for the expected number of cases in 2020 at the province level under maintenance of current intervention strategies, as well as current interventions combined with the introduction of various levels of vector control. By comparing the effect of model structure and model fitting procedures on the predictions, we are able to provide a range of uncertainty in model prediction. Both models predicted that continuing current intervention will achieve elimination of HAT as public health problem in most health zones of former Equateur and that introducing moderate vector control could enable elimination as public health problem by 2020 and full elimination by 2030 in all health zones.

2. Methods

2.1. Data

Former Equateur province had an area of 403,292 km^2 and a population of approximately 7.5 million inhabitants. In 2015 this province was divided into five smaller provinces: Nord-Ubangi, Mongala, Sud-Ubangi, Equateur and Tshuapa; however, given that our data comes from before this division, we focus on the whole of the former province. Former Equateur province was subdivided into smaller administrative units called "zones de santé" or "health zones", which each have a population size of approximately 100,000 people, although there is one as small as 34,000 and another as large as 327,000. For each health zone considered, the two teams calibrated their models independently to the aggregate incidence of actively- and passively-detected cases and the number of active screenings between 2000 and 2012 as recorded in the WHO HAT Atlas (Simarro et al., 2010; Simarro et al., 2015).

In order to ascertain which data belonged to a particular health zone, assigned geo-locations were used to match each reported active screening or passive detection to the 2014 health zone map. This was to resolve issues with changing health zone boundaries throughout the period 2000–2012. For data with no assigned geolocation, village names and other information such as "aire de santé" (health areas, which are smaller divisions within health zones) were matched to data with assigned geo-locations. For the few data that could not be matched, the original health zone name was used as a proxy for the 2014 health zone.

Of 69 health zones in the former Equateur, 12 had no reported cases or active screening, and were therefore not included in the model fitting process (SI2 provides maps of the health zones which were fitted to in this study). These health zones with no reported cases were assumed to have already met the zero transmission goal, however it is noted that without active screening or information about the passive surveillance system in these zones, there is some uncertainty about whether there is underreporting or if these are truly zones with zero infection. Neither group had previously fitted their models to data from former Equateur province.

2.2. Models

The independent teams previously developed their own deterministic models (Rock et al., 2015b; Pandey et al., 2015) and

variants of these were used to perform this analysis. The two models structures are based on different hypothesis regarding disease progression, human risk and behaviour.

Gambian HAT has typically been considered to be an anthroponotic disease, with no animal involvement in transmission. Previous work by both research teams did not provided support for either anthroponotic transmission or animals as infection reservoirs in former Bandundu province of DRC (Rock et al., 2015b), or in Guinea (Pandey et al., 2015). In this study, both teams selected models that had human-tsetse transmission only.

Both models are deterministic and compartmental, with classes for susceptibles, those in stage 1 and 2 disease, those recovering from infection, and explicit tsetse dynamics. Model W is a previously published model (Rock et al., 2015b), which accounts for heterogeneity in both human exposure to tsetse bites and also screening participation. In line with model fitting results to health zones from former Bandundu province of DRC, this model assumes that the high-risk people do not participate in active screening although the proportion of people in these categories and the relative exposure are re-fitted for each health zone in former Equateur as this is likely to vary geographically. An adaptation to this model simulates the impact of tiny tsetse targets on fly populations and subsequent disease dynamics in humans (Rock et al., 2017). Model Y is an extension to a previously published model (Pandey et al., 2015) and now includes asymptomatic human infection, which progresses to self-cure rather than disease. It is assumed that such asymptomatically infected individuals are able to transmit the parasite to tsetse with a reduced probability. Both models are described further in the SI1 (Model Description).

2.3. Fitting and validation

The teams used the data of the number of people actively screening for all years (2000–2012) in every calibration, however they conducted a 3-stage calibration/uncensor procedure whereby the teams only used 2000–2006 reported case data (both active and passive) for the initial model fit. Once the first stage was complete, case data from years 2000–2009 were used by the teams to repeat the model calibration. Finally, the full data set was uncensored and the models were calibrated for a final time. The three rounds of fitting were performed in order to be able to conduct model validation and to assess the models' predictive abilities.

Both teams used the same estimated population size of each health zone in 2014 (see SI2 Fitting and Prediction for these values) and an assumed population growth of 3% per year which is the standard used by the national vaccination campaign (OCHA, 2016). All other parameters, the model structure, and the method for model fitting were chosen by each group independently. Model W, which had four unknown parameters, was fitted using Markov chain Monte Carlo (MCMC), whereas Model Y used Bayesian melding technique to calibrate their six parameters. Each of the fitted parameters for both groups represented a biological quantity (such as a probability of transmission), or a behavioural one (such as who was actively screened). Initial conditions were taken as endemic equilibria in the absence of active screening or vector control as it was assumed that this was the only intervention available before 2000 (see SI1 for more model fitting details). Each group provided sufficient model replicates using their respective fitting algorithm to generate a distribution of fitted/predicted active and passive case numbers for years 2000–2012. Model Y was fitted using a mixture of Poisson and Binomial likelihood function, whereas Model W was fitted using just Binomial likelihood functions; however given the population sizes this was not likely to generate significant differences. The level of uncertainty around the model fitting determined the level of confidence in the model predictions.

Table 1
Six intervention strategies under consideration in this analysis.

Strategy	Tsetse population reduction after 1 year (starting in 2017)	Active screening level
1	0%	Mean (for each health zone) of 2000–2012 level
2	0%	Max (for each health zone) of 2000–2012 level
3	60%	Mean
4	60%	Max
5	90%	Mean
6	90%	Max

2.4. Projections

Following fitting, each group generated projections (from 2013) to simulate the predicted year of (a) elimination as a public health problem; and (b) full elimination, for each health zone under 6 different intervention strategies (Table 1). The simulated strategies encompass current interventions (Strategies 1 and 2) and readily available interventions (Strategies 3–6). Using these projections, the teams assessed whether the current strategy (variable active screening on top of passive surveillance) is sufficient to achieve HAT elimination as a public health problem by 2020, and full elimination by 2030 in Equateur and whether additional vector control could facilitate attaining these goals. Both groups assumed that passive surveillance would continue with the same detection rate post-2012 as pre-2012.

As vector control has not been implemented at scale in this province previously, it is unclear what the efficacy of vector interventions could be in the region. A range of different tsetse control interventions is available and includes targets, traps and insecticidal treated cattle. Each of these methods would be expected to have similar impact on the disease dynamics if the same tsetse reduction was achieved, although the effort required and costs of these different methods vary greatly and are setting-dependant (Shaw et al., 2013). As a focussed example, in this study both groups modelled the impact of tiny targets on tsetse populations and disease dynamics. In other settings tsetse control via tiny targets has been found to reduce populations rapidly; in Guinea 80% tsetse population reduction was achieved 18 months after initial implementation (Courtin et al., 2015) and in Uganda 90% reduction was observed after 1 year (Tirados et al., 2015). The teams therefore selected two plausible tsetse population reductions, 60% and 90%, that might be attained following a year of target implementation and correspond to moderately and highly effective tsetse control.

Due to their use of deterministic modelling, both groups had to select a suitable criterion for elimination. Since the definition of elimination as a public health problem relates directly to reporting rather than transmission *per se*, both groups used the threshold of the reported case incidence below 1 per 10,000 at a health zone level as the criterion for this target. The health zone level was chosen as it is a clearly defined administrative unit with population size estimates available, whereas a "HAT focus" is more ambiguous both spatially and in terms of demography. For full elimination, the teams agreed to compute the full elimination year as the first year in which a given health zone would reduce their incidence to <0.5 new infections per year across the entire health zone. This slight modification to the true elimination goal was necessary because of the deterministic nature of the models; at less than half an infection per year stochastic elimination is extremely likely. It is noted that new transmissions and new reported cases are distinguished by the time lag between infection and detection for both models. Model W also accounts for underreporting in passive detection data (see SI1), which creates even greater differences between transmission and reporting.

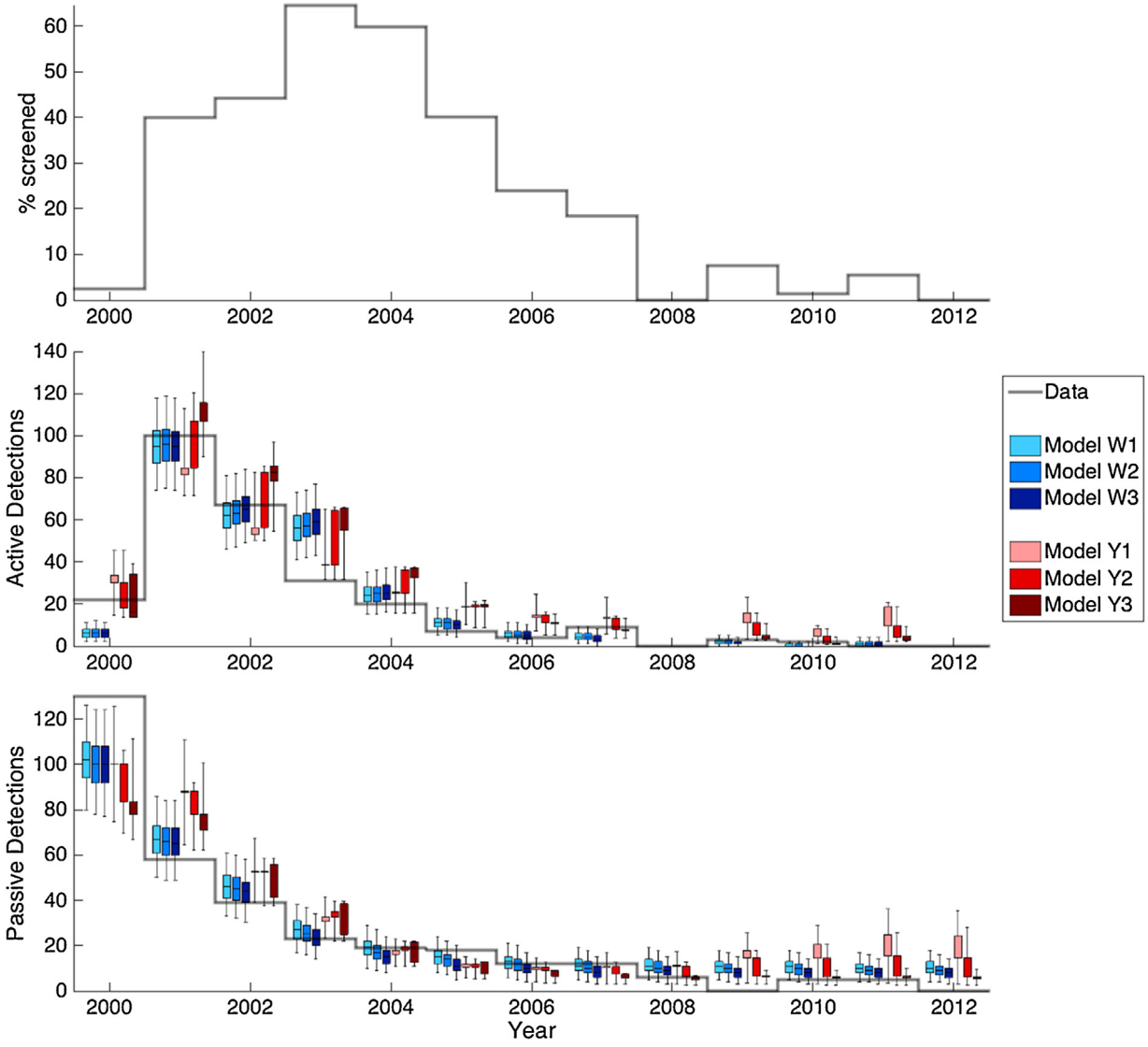

Fig. 1. Example model fitting to Budjala (health zone 18). The top graph shows the level of active screening achieved in each year in this health zone, the middle and bottom show the number of cases found actively and passively respectively. On these, the data is shown as a grey line, whilst results of fitting Models W and Y across all rounds (1–3) are given as box and whisker plots with the whiskers representing 95% credible intervals. In round 1 (results W1 and Y1), the available case data was only years 2000–2006; the remaining years shown are model predictions using known active screening numbers (and no vector control). Likewise, round 2 shows fitting for 2000–2009, whilst round 3 uses all years (2000–2012) for fitting.

3. Results

3.1. Fitting and validation

Censoring was performed in order to test the models' predictive power. Results of fitting in each of the 57 health zones can be seen in SI2. Model Y typically remained relatively consistent in its projections across the 3 fitting and projection rounds. In contrast, during the initial round of fitting Model W was found be unable to replicate reliably the trend in observed active cases; in particular the number of observed cases were often well below the predicted number of false positives. As a result the specificity parameter was changed from 99.9% to 100% in rounds 2 and 3, leading to a substantial improvement in the fit in these rounds for many health zones. Results from Model W used in comparison figures (main text and SI2) show the 100% specificity across all rounds, but the impact of changing specificity is shown in SI3. For example in Bwamanda (health zone 22) using an imperfect 99.9% specificity test would result in many false positive detections in 2002–2006 due to the high screening coverage (Figs. S3–22). In reality there was a decreasing trend in active case reporting, which was reflected in fitting the model with 100% specificity (shown in green) where it could not be produced using 99.9% specificity (purple). Model W rounds using 100% specificity were typically very similar in their projections.

In some health zones, extra data in later years did impact the model fits, e.g. in Bikoro (health zone 4), there were peaks in active detections in years 2009 and 2011. In Iboko and Ntondo and (health zones 27 and 51) there were 0 and 1 total detections respectively prior to 2006 and so the results of fitting changed for both models after round 2, when more years were uncensored. The change was more stark for Iboko (health zone 27) as no active screening took place pre-2006. In Ntondo (health zone 51), there were screenings in 2000 and 2003 (both covering <6% of the population), which this resulted in less difference between rounds 1 and 2 for active screening, but still substantial differences for passive.

One clear discrepancy between the modelling approaches was how to deal with health-zones where there were limited data. In

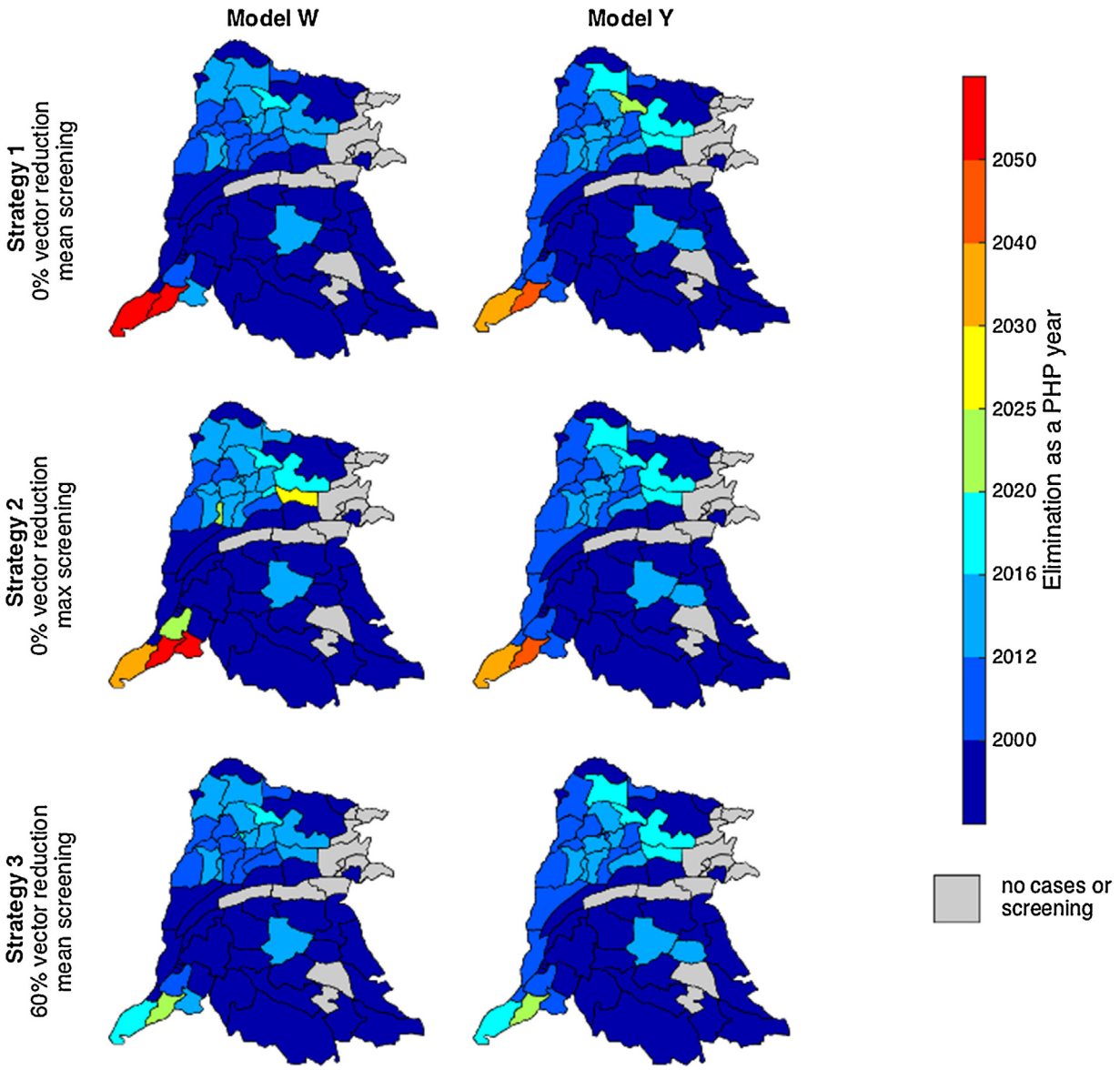

Fig. 2. Median elimination as a public health problem (PHP) years by health zone under strategies 1–3 as predicted by the two models, Model W on the left and Model Y on the right. Maps for all six strategies under each of the models are given in the SI2.

14 health zones there was limited (and temporally patchy) screening and no reported cases, therefore, Team Y decided not to include model fitting results for the full elimination years in these 14 health zones in the study, as they are likely to have already reached full elimination. Team W fitted their model in all health zones and found that in these health zones, the best model fit was obtained with the basic reproductive ratio (R_0) less than one (i.e. no sustained local transmission). In the 12 health zones with no reported cases or active screening neither team fitted their model, and it was assumed that there was no transmission in these health zones.

Both fitting approaches lead to quite tight credible intervals (CIs) in most cases (Fig. 1).

3.2. *Predictions from models (using all available data)*

Model W predicts that, on average, 2 of the 69 health zones do not to achieve elimination as a public health problem by 2020 if the mean level of screening is continued (Fig. 2). Somewhat counter intuitively, this increases to 6 health zones with maximum screening. This is explained by the increase in screening effort, and therefore more cases being detected in the four additional health zones which fail to meet the target. Using the median result of Model Y, simulations indicate that all but three health zones are on track to achieve elimination as a public health problem by 2020 if mean screening levels continue (Fig. 2); this decreases to two if maximum screening continues.

Changing strategy was predicted to have little impact in most health zones under both models due to almost all of them already being on track. Under strategies with at least 60% vector reduction, Ntondo (health zone 51) was the only health zone not on target to reach the goal. For the health zones that Model W suggests wouldn't meet the target by 2020 under mean screening, increasing screening had little impact the projected elimination year, however introducing moderate (60%) vector control reduced the timescale and just one health zone (Ntondo, health zone 51) was found not to meet the target (Fig. 2) and highly effective tsetse control (90%) combined with maximum screening lead to all health zones achieving elimination as a public health problem by 2020. Results from Model Y indicate that Ntondo (health zone 51) could still fail to meet this target even with such effective tsetse control.

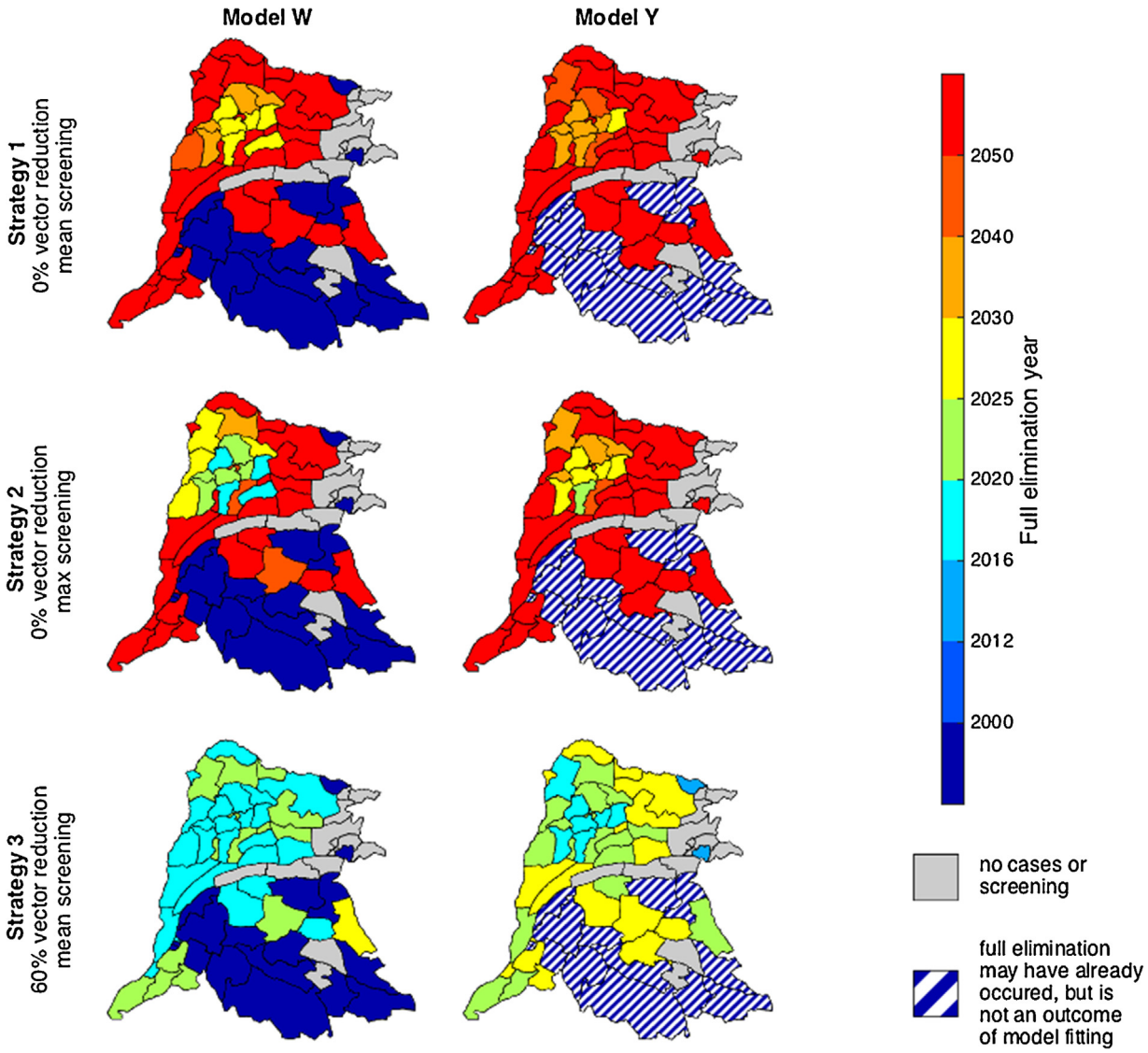

Fig. 3. Median full elimination years, by health zone under strategies 1–3 as predicted by the two models, Model W on the left and Model Y on the right. Striped regions were assigned through direct assessment of the data rather than by model fitting. Maps for all six strategies under each of the models are given in the SI2.

It was predicted that 34 and 42 of the 69 health zones (Models W and Y respectively) would not to meet the full elimination goal by 2030 under mean screening (Fig. 3). Increasing to maximum screening showed improvements under both models with a reduction to 27 and 37 health zones behind schedule for stopping transmission (Fig. 3). Introducing moderate vector control alongside mean screening levels had a marked impact on model predictions with Models W and Y predicting that all health zones would have stopped transmission by 2030 (Fig. 3). Both teams found that achieving 90% tsetse reduction in all health zones resulted in province level full elimination by 2025 due to the impact of vector control on new transmissions (SI2 Figs. S2–5 and S2–7).

Vector control generated large improvements in the projected elimination years for both teams (Figs. 4 and 5). For both teams, the proposed vector reductions are predicted to reduce the time to elimination by several decades in many health zones where the time to elimination is long under current strategy.

Figs. 4 and 5 show the probability of achieving <1 reported case per 10,000 by 2020 and zero transmission by 2030 respectively. In most health zones and under most strategies the models have high certainty that the goals will either be meet (>90% chance shown in dark blue) or won't be meet (<10% chance shown in dark red). However, for a few health zones, particularly in relation to full elimination, there is much more uncertainty whether these targets will be met and so these are take colours from the middle of the spectrum.

Table 2 gives the expected number of reported cases in 2020 for the whole of former Equateur province under the six different strategies. Model W predicts slightly higher numbers of cases in 2020 under intervention without vector control (Strategies 1 and 2), however it is expected that even under mean screening alone there will be fewer than 300 cases in former Equateur. Both teams predict that there are likely to be fewer than 120 reported cases if vector control is implemented (Strategies 3–6) which would comprise <6% of the global goal total. The models agree that adding or increasing vector control is always beneficial to the reduction in transmission, however the number of cases predicted in 2020 under Model W increases with increased screening alone due to increased detection effort. Under vector control, Model W predicts that improving vector control from 60 to 90% is better than increasing screening levels from mean to maximum (i.e. moving from Strategy 3 to 5 is better than 3 to 4), conversely Model Y

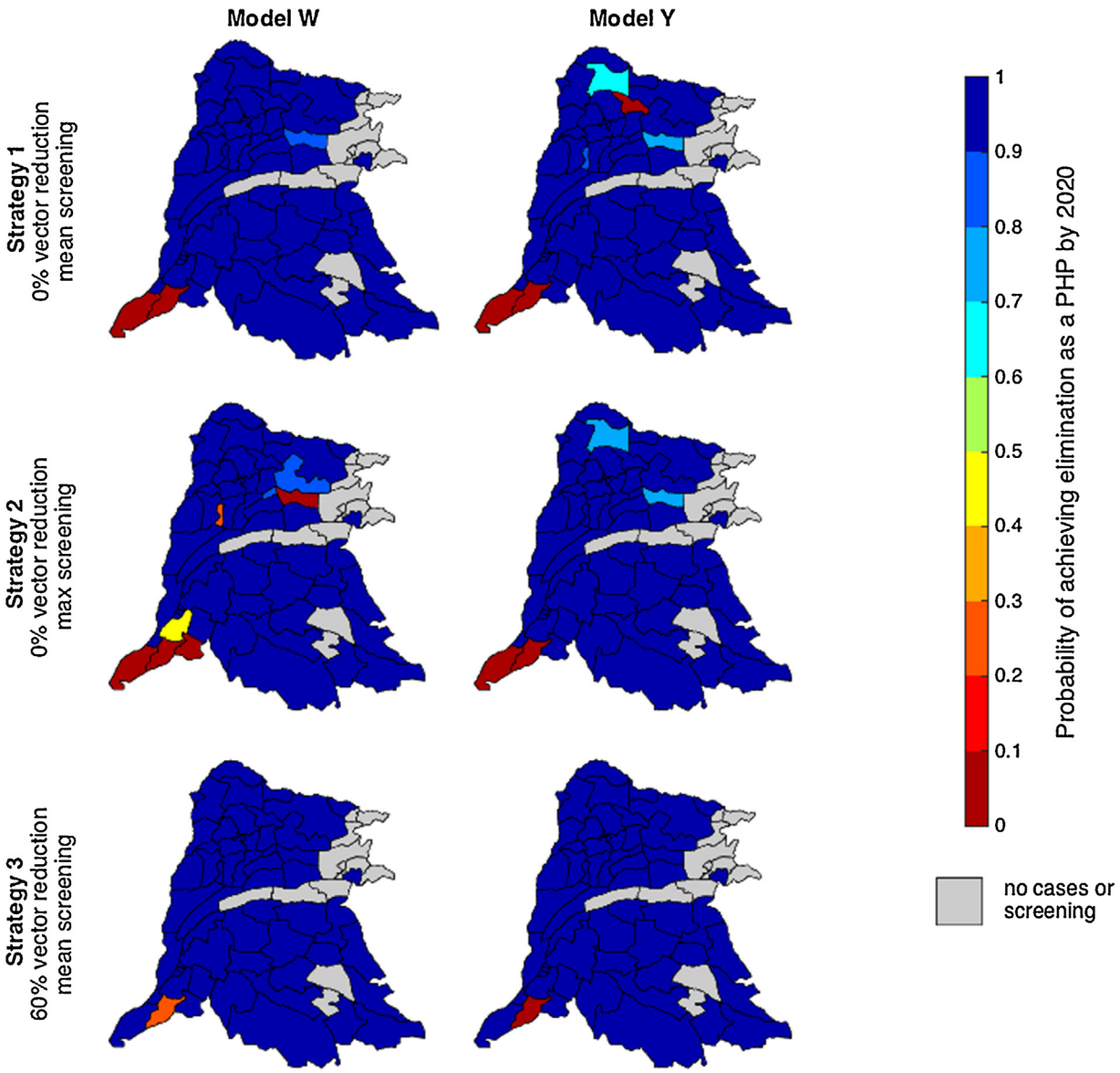

Fig. 4. Probability of achieving elimination as a public health problem by 2020 by health zone under strategies 1–3 as predicted by the two models, Model W on the left and Model Y on the right. Maps for all six strategies under each of the models are given in the SI2.

Table 2
The predicted number of total reported cases (median and 95% CIs) across former Equateur province in 2020 under all strategies.

	Total predicted reported cases in former Equateur in 2020	
Strategy	Model W	Model Y
1. Mean screening only	278 (242, 316)	239 (210, 272)
2. Max screening only	283 (240, 330)	201 (172, 231)
3. Mean screening + 60% VC	63 (48, 80)	117 (100, 136)
4. Max screening + 60% VC	54 (39, 69)	80 (64, 99)
5. Mean screening + 90% VC	38 (26, 51)	93 (77, 108)
6. Max screening + 90% VC	29 (19, 40)	55 (43, 68)

projects lower case numbers under increased screening (80 cases) compared to better vector control (93 cases).

The summary results for both elimination as a public health problem and full elimination are given in Figs. 6 and 7 and also show where there is consensus between models. It is noted that, for elimination as a PHP (Fig. 6), both models agree that many of the health zones will achieve the 2020 goal of <1 reported case per 10,000 by using strategies without vector control. Only two health zones (in the South West) are identified in both models as failing to achieve the 2020 goal. In general Model W tends to be more pessimistic about the effects of increasing screening, while Model Y tends to be more pessimistic about the effects of adding vector control; but, in general, the degree of agreement is high. It is observed that many health zones are projected by both models to not achieve full elimination before 2030 if current strategy is continued (Fig. 7), however with 60% or more vector control, all health zones are predicted to meet this goal. Model W is more optimistic about the proportion of health zones which may need improved strategies, however many of the health zones, for which full elimination is predicted post-2030, have extremely low case numbers.

4. Discussion

Two independent models were used to assess the progress towards elimination of Gambian HAT in former Equateur province,

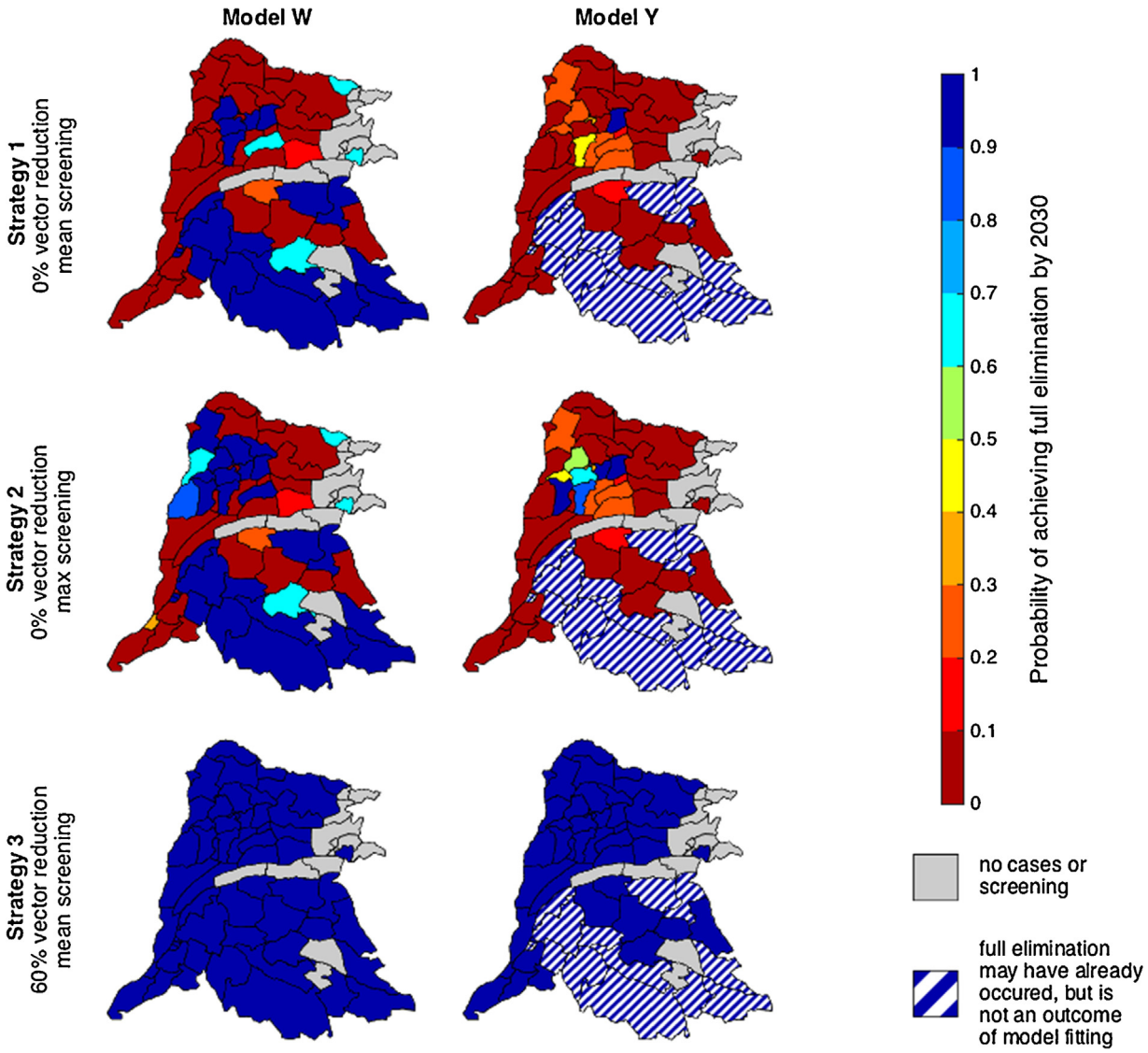

Fig. 5. Probability of achieving full elimination by 2030 by health zone under strategies 1–3 as predicted by the two models, Model W on the left and Model Y on the right. Striped regions were assigned through direct assessment of the data rather than by model fitting. Maps for all six strategies under each of the models are given in the SI2.

DRC. Despite their structural differences and fitting methodologies the models agreed that most health zones within the province are on track to achieve the elimination as a public health problem by 2020 if active screening continues at the mean level achieved between 2000 and 2012. Results from both models indicate that Ntondo and Lukolela (health zones 51 and 39) are least likely to achieve elimination as a public health problem by 2020 (Figs. 2, 4 and 6) and will likely contribute around 10–11% and 11–15% of the cases for the whole province in that year respectively. In Gemena (health zone 26), active screening appears to have substantially reduced reported case numbers, but a drop-off in screening coverage for most of 2008 onwards could lead to a persistent number of low cases as is suggested by the results of fitting both models (Fig. S2–33). In Lukolela (health zone 39) there was an initial drop in passive case detection following the start of the active screening campaign, however since 2003 the passive case numbers have plateaued (Fig. S2–46). Again, the level of screening achieved declined after the first four years and coverage was quite low for the remainder of the time. Both teams determined that increased levels of screening may be sufficient in some health zones to achieve the 2030 goal, however vector control could have a substantial beneficial impact on reducing the time until full elimination.

It is noted that levels of screening achieved across former Equateur province as a whole have fluctuated between 2000 and 2012, with the highest percentage of people screened (12.0%) occurring in 2003 and a mean of 6.2% during the whole time period. In later years the number of people screening has decreased and in 2012 just 1.3% of Equateur took part in active screening. For most health zones, continuing with the mean screening level represents an increase from that achieved in 2012.

It is important to note that the considered strategies are based on plausible intervention strategies using current tools. Active screening capacity was based on historic screening for the health zone. Since data was only available up to 2012, screening interventions during the years 2013–2016 had to be predicted, despite having already occurred. Vector control was only assumed to take place from 2017. Large changes in the level of active screening between 2013 and 2016 would be likely to shift model predictions. In particular for health zones which are expected to achieve either elimination target during this time period, e.g. Befale or Kungu (health zones 3 and 32), these predictions have been made conditioning on screening having continued at similar levels to 2000–2012.

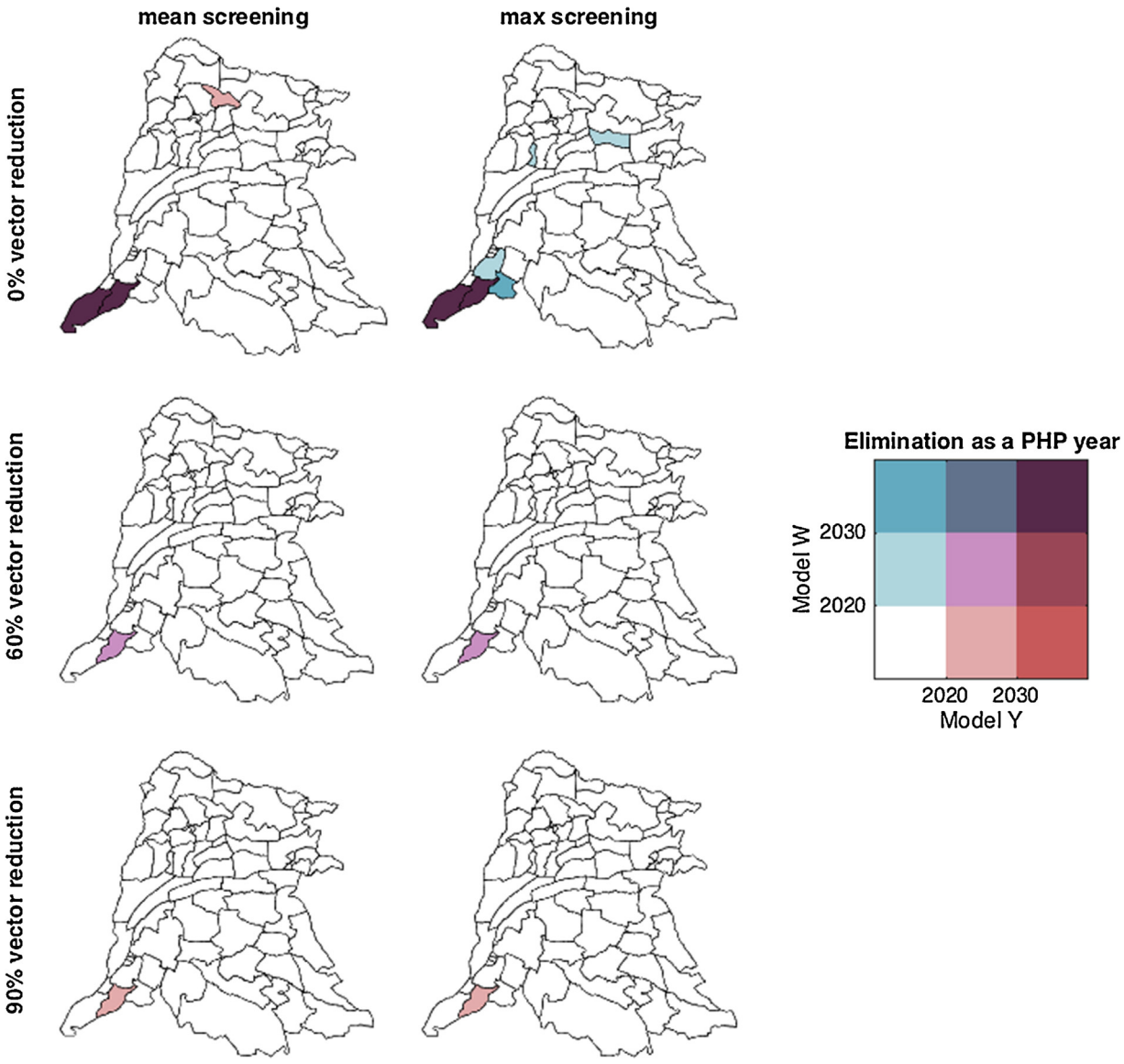

Fig. 6. Bivariate-chronopleth comparison map showing consensus/disagreement between the modelling results for elimination as a public health problem (PHP) (<1 new reported case per 10,000 per year). Each row denotes a different level of vector control, and each column, a different level of active screening. These show the results under round 3, which uses case data from all available years (2000–2012), projected forwards with the six different strategies. Colours denotes when elimination as a public health problem is predicted to occur under each model; either pre-2020, between 2020 and 2030, or post-2030. Blue shades are for health zones in which Model W yields later elimination years, red shades are for health zones in which Model Y yields later years. The darker the colour, the later the predicted year. Purple and white health zones are where there is consensus between the two models, with darker colours for health zones which are expected to achieve the goal later.

There are differences in the model results, with Model W projecting that Bangabola, Bikoro, Bosomanzi, Iboko, Lukolela and Ntondo (health zones 1, 4, 16, 27, 39 and 51) may not be on track to achieve elimination as a public health problem by 2020, whereas Model Y predicts that this should be feasible under current (medical) interventions excluding Loko, Lukolela and Ntondo (health zones 37, 39 and 51). Model W shows that for four health zones, increasing screening level would postpone the year to elimination as a public health problem because the increased screening would lead to increased reporting, however this would ultimately reduce underlying transmission in these regions; this effect was not observed for Model Y.

There are a few health zones in which the models appear to completely differ in their full elimination predictions. For example in Bumba and Yakoma (health zones 20 and 55), Model Y predicts the full elimination won't be achieved until after 2050 under Strategy 1, yet Model W predicts this could occur before 2020. In fact, Model Y predicts that this health zone will see an extremely low number of cases, however it will still not be sufficient to completely stop transmission (Fig. S2–27 and S2–62). It is difficult to establish from these data whether some health zones with very low screening have on-going transmission in the region rather than importations. Both teams emphasise that additional active screening data would help to determine whether such areas have active transmission or not. This demonstrates the challenges of projecting forwards from extremely low case numbers.

Across all model predictions, vector control impacted the time until zero transmission so that this goal was achieved within a few years of implementation of tiny targets. Some health zones have predicted elimination years which greatly exceed 2020/2030 despite relatively low prevalence. This is indicative of areas which have seen little change to the incidence between 2000 and 2012 and without changing to an alternative strategy (such as increasing screening or improving passive detection) the modelling predicts

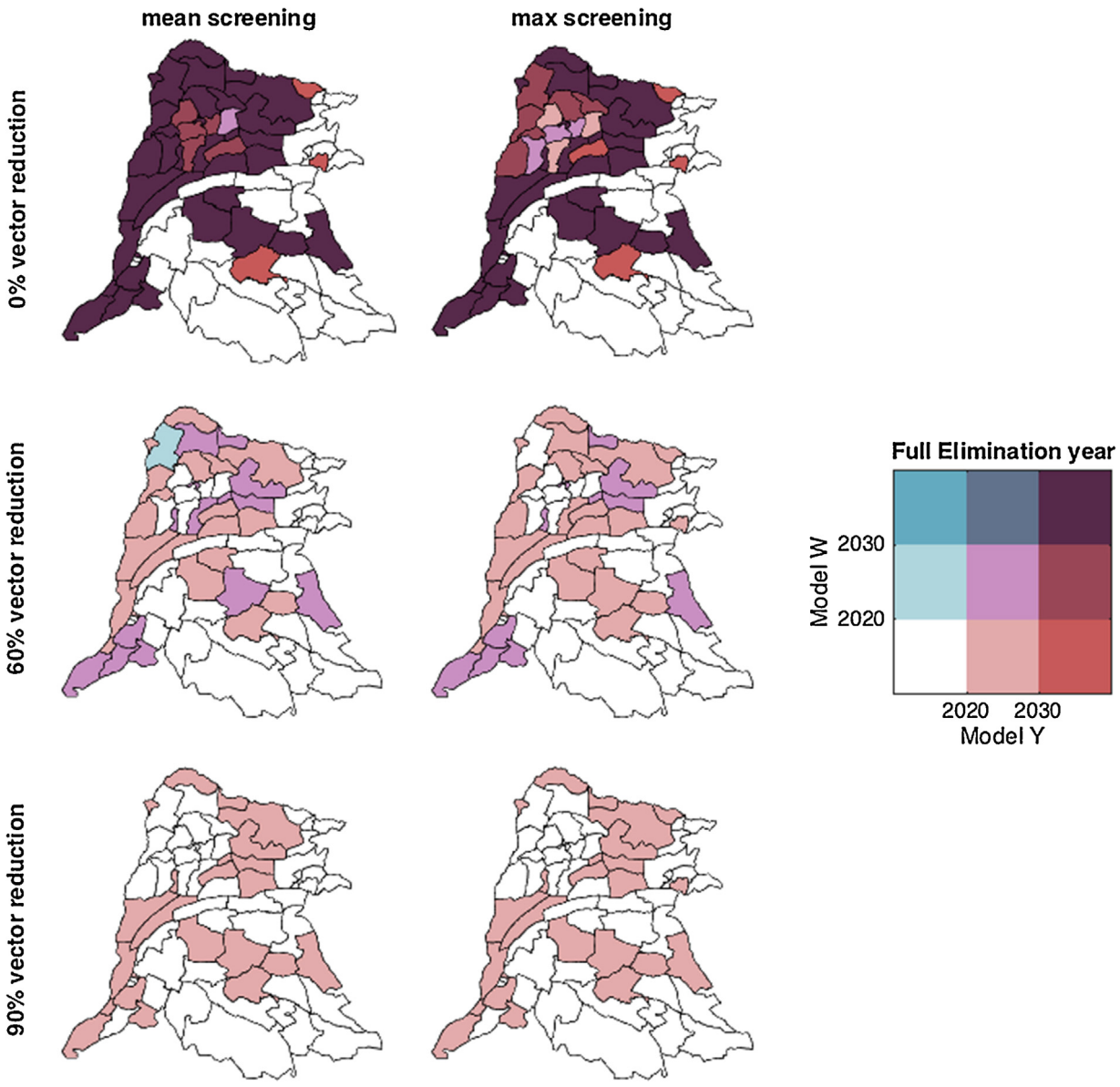

Fig. 7. Bivariate-chronopleth comparison map showing consensus/disagreement between the modelling results for full elimination. Each row denotes a different level of vector control, and each column, a different level of active screening. These show the results under round 3, which uses case data from all available years (2000–2012), projected forwards with the six different strategies. Colours denotes when full elimination is predicted to occur under each model; either pre-2020, between 2020 and 2030, or post-2030. Blue shades are for health zones in which Model W yields later elimination years, red shades are for health zones in which Model Y yields later years. The darker the colour, the later the predicted year. Purple and white health zones are where there is consensus between the two models, with darker colours for health zones which are expected to achieve the goal later.

the HAT cases will persist at this level. For example Mompono, Gbado-Lite and Mobayi Mbongo (health zones 46, 25 and 45) are expected to have transmission past 2030 despite indications that some could achieve elimination as a public health problem by 2020.

No model is perfect – they represent an abstract conceptualisation of the real world and approximate many of the complex processes. In this study, it is observed that more data improves the model fits, however, the improvement is slight for most health zones as even early data provides a good indicator prediction of long-term dynamics. Aggregate data was used at a health zone level (approximately 100,000 population size) and also at a yearly temporal resolution. The unknown timing of both active screenings and passive detections could have impacted model fitting. Likewise, by using aggregate health zone data, small-scale spatial heterogeneities could have been missed. Health zone population size estimates may not be reliable, but this demographic denominator is an important factor in modelling. If the number of people in a health zone is significantly higher or lower than the estimate, then model fitting could indicate the controls are much more or less effective than they are in reality. Human movement between health zones and, in particular, from outside the region was not accounted for in either model due to lack of data. It is important to consider the impact of human migration on persistence of HAT infection into a region in the planning the end-game strategy, this is particularly the case for health zones sharing boundaries or those which see large influx into the region. Other factors such as changing awareness of disease in the region, which corresponds to the passive detection rate, could impact the accuracy of model fits where this type of parameter is assumed to be constant over time.

In this study, both models used deterministic framework to simulate disease dynamics. In future work it would be beneficial to consider the impact of chance events on local disease extinction by

using stochastic models. This type of approach can be particularly relevant when considering the small number of cases prior to full elimination and avoids the need to define the cut-off threshold that is necessary for deterministic models.

Tsetse control has not previously be implemented in this region and it is unclear what impact vector control such as tiny targets might have on vector densities in Equateur. Values comparable to Uganda (90% reduction) and lower than Guinea (60% reduction) were used as a guide for the potential impact of tsetse control. It is noted that some isolated populations can potentially achieve even greater results, as observed with the tiny target intervention in the Mandoul focus of Chad which had a 99% reduction (Mahamat et al., 2017). Tiny targets have been estimated to achieve control of tsetse populations at a cost of US$ 84/km^2 (Shaw et al., 2015) which is cheap compared to other methods including traps (US$ 283/km^2) and spraying (US $380/km^2) (Shaw et al., 2013). In some settings, insecticidal treated cattle has been found to be the least expensive option (US$30/km^2) and more easily accepted by famers (Shaw et al., 2013; Shaw et al., 2014; Muhanguzi et al., 2015 Muhanguzi et al., 2015), however the low density of livestock in former Equateur province means this would be an impractical option for this region of DRC. Whilst models of different types of vector control might be structurally different to those presented for this study, if another method of vector control was used in former Equateur and also reduced tsetse populations by 60% or 90% after a year, the expected outcome in terms of human infection dynamics would be very similar.

Making predictions for areas where there were no reported cases is challenging. If no screening was performed and no passive cases were reported it is hard to provide realistic predictions for the elimination years due to a large amount of uncertainty. For some areas which have had little active screening, a better intervention strategy could simply consist of higher screening levels. Another tool which is considered important in the elimination of Gambian HAT is improvements to the passive surveillance system by providing more local health facilities with HAT diagnostics such as rapid diagnostic test kits which do not need a cold-chain. This has been implemented in other regions of DRC where active screening is arduous (FIND, 2016) and will become increasingly important as other control measures are reduced or removed to ensure recrudescence does not occur. In the future safer, oral drugs (in particular stage-independent treatment) and improved diagnostics will likewise provide useful tools in the end-game for HAT and contribute to a shift in the way HAT infection is diagnosed, treated and monitored.

This analysis concludes that former Equateur province is largely on track to meet the key goal of elimination as a public health problem by 2020, although some health zones may need to improve active screening levels and/or add additional interventions such as vector control to meet this target. It is important to remember that, at present, only one human infectious disease, smallpox, has been eradicated and whilst others including polio and Guinea Worm will hopefully follow suit within the next few years, the effort and time required to reach such low case numbers was underestimated. In former Equateur province of DRC, the difficulty of successfully stopping transmission is demonstrated through these model simulations in which between 49 and 61% of health zones (on average) are unlikely to meet the 2030 goal if active screening continues at its mean level and 39–54% of health zones continuing with maximum screening. Additional vector intervention appears to be one very promising method to reach full elimination rapidly. Model simulations with 60% vector reduction and just the mean screening level project that all health zones will meet the full elimination target, and see this occur more rapidly with higher levels of screening and/or greater reduction to tsetse populations. This modelling suggests that, as with other diseases which are targeted for elimination or eradication, the end-game strategy will undoubtedly have to adapt to ensure the success of the elimination goal.

Author contributions

Conceived of the study: KR.
Original data collection: CL.
Drafted manuscript: KR, MK.
Developed models: KR, MK, AP, MNM, AG, KA.
Performed model simulations: KR, MK, AP, MNM.
Conducted analysis: KR, MK, AP, MNM.
Edited manuscript: KR, MK, CL, AP, AG, MNM, KA.
Drew graphs and maps: KR.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2017.01.006.

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