The potential impact of programmes interruptions due to COVID-19 on 7 neglected tropical diseases: a modelling-based analysis

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NTD Modelling Consortium

Executive Summary

Background: The spread of SARS-CoV-2 (COVID-19) will impact the progress of neglected tropical disease (NTD) programmes. In the short term, World Health Organization (WHO) guidance advises that many NTD surveys, active case finding activities, and mass drug administration (MDA) campaigns should be postponed, whilst support for prompt diagnosis, treatment, and essential vector control should continue where possible (WHO, 2020). Understanding if these interruptions will erode previous gains and, therefore, what can be done to prevent or make up for increases in transmission or resurgence, is essential. This report describes mathematical modelling insights on how NTD programmes could be impacted by the interruption of interventions and what remedial strategies could be implemented once programmes resumes.

Questions posed in this report: How much delay programmes can tolerate before they start seeing a negative impact in achieving the 2030 goals? In which settings will delay-related impacts be greatest? What remedial strategies can be implemented once programmes resume to mitigate the impact of delays?

Summary:

- The underlying disease dynamics for each NTD, as well as the transmission setting, will impact the rate of resurgence that programmes will face during this delay due to COVID-19.
- Our analyses suggest that many NTD programmes should be able to recover from a brief delay particularly when the rates at which infection resurges are slow in the absence of interventions.
- However, longer delays will require more intensive remedial strategies to get back on track and will translate into greater accrued burden of morbidity.
- High transmission areas face the greatest risk, as resurgence will be high in these areas.
- Amongst the diseases for which MDA is the main intervention, trachoma and schistosomiasis are likely to see the quickest bounce back, particularly in high transmission areas.
- More intensive remedial strategies are, therefore, required for trachoma and schistosomiasis such as extra rounds of MDA or changing the MDA target population, respectively, to resume or even to accelerate progress towards the 2030 goals.
- There is an increased risk of undetected outbreaks of visceral leishmaniasis in the Indian sub-continent and hence active case detection activities should resume as soon as possible to detect any increase in underlying infections.

Local context: The results outlined here are average results for general scenarios, and the actual impact will depend on the local context. For example, the stage and effectiveness of the programmes will also play a role in the resurgence rate. Programmes in their early stages will return towards pre-treatment endemicity levels more quickly, whereas programmes in later stages - which have managed to reduce/control transmission - will experience lower levels of resurgence, provided the residual transmission rate is not too high.

Disease-specific impact on reaching the goals: In Table 1 below we summarise the expected impact on the achievement of the 2030 goals for 7 NTDs. This highlights the different impacts on NTDs with different biologies. Following the table, each disease is discussed in turn, including descriptions of the methodology and key assumptions of the analysis, as well as the empirical evidence from previous interruptions (e.g. due to the Ebola outbreak in West Africa).

Table 1: Impact of 1 year of interruption in programmes on the achievement of the 2030 goals for 7 NTDs.

Disease (Goal - elimination of transmission (EOT) or elimination as a public health problem (EPHP))	Minimum average impact and type of setting where this would be seen	Maximum average impact and type of setting where this would be seen	Minimum catch up strategy	Notes
Soil-transmitted helminthiasis (EPHP)	1 year (hookworm, 20-50% prevalence)	<2 years (*A. lumbricoides* and *T. trichiura*, 20-50% prevalence)	Additional round of community-wide treatment	High prevalence settings unlikely to reach 2030 target regardless of interruption unless adults are treated (hookworm) or dual treatment with ivermectin is implemented (*T. trichiura*)
Schistosomiasis (*Schistosoma mansoni*; EPHP)	No impact (<10% prevalence)	2 years (>50% prevalence)	Additional treatment round in moderate and high prevalence settings	High prevalence settings may not be on track for EPHP by 2030 unless adults are also treated. Postponement has a lower impact in high adult burden settings.
Lymphatic filariasis (EPHP)	No impact (<10% current prevalence)	1 year (15-20% current prevalence)	1-year biannual treatment OR 3 years enhanced (80%) coverage OR 1 year of IDA	Most settings will see a one-year delay in reaching EPHP but should still achieve the target by 2030. Settings with high baseline prevalence (>25%) and start of MDA after 2017 are at increased risk of not achieving the goal by 2030

Disease (Goal - elimination of transmission (EOT) or elimination as a public health problem (EPHP))	Minimum average impact and type of setting where this would be seen	Maximum average impact and type of setting where this would be seen	Minimum catch up strategy	Notes
Onchocerciasis (EOT)	No impact (≤40% baseline prevalence, and/or long treatment duration)	Modest impact (>40% baseline prevalence and shorter treatment duration)	1-year biannual treatment in 2021 helps the programmes to get back on track (65% coverage; 5% non-adherence)	Two years of MDA interruption has a larger impact for higher prevalence settings and shorter treatment histories; biannual treatment in 2022 and 2023, or increased coverage mitigates the impact of interruption
Trachoma (EPHP)	<1 year (mean 20% TF prevalence)	>2 years (mean 40% prevalence TF)	Additional treatment round in high prevalence settings	Opportunity to not just catch up, but accelerate in trouble areas
Visceral leishmaniasis in the Indian sub-continent (EPHP)	~1.5 years (in previously highly endemic settings with 1-year interruption of the programmes during the attack phase)	~2 years (in previously moderately endemic settings with 1-year interruption of the programmes during the attack phase)	Extending the attack phase could reduce the impact caused by Covid-19 in highly endemic settings	In settings that have already achieved EPHP previously to the Covid-19 pandemic, VL incidences can increase to above the target again
Gambiense human African trypanosomiasis (EOT)	No difference to EOT year (but some increase in deaths)	3 years (2-year interruption)	None	High-transmission settings may not reach 2030 target regardless of interruption

List of Abbreviations

ACD	Active case detection
DALY	Disability-adjusted life year
DRC	Democratic Republic of the Congo
EOT	Elimination of transmission
EPHP	Elimination as a public health problem
F&E	Facial cleanliness & environmental improvement
GET2020	Global Elimination of blinding Trachoma
gHAT	Gambiense human African trypanosomiasis
IDA	Ivermectin + DEC + Albendazole
IRS	Indoor residual spraying (of insecticide)
ISC	Indian sub-continent
LF	Lymphatic filariasis
LMIC	Low- and middle-income countries
MDA	Mass drug administration
MoH	Ministry of Health
mf	Microfilarial
NTD	Neglected tropical disease
PC	Preventive chemotherapy
pre-SAC	Pre-school-age children
R_0	Basic reproduction ratio
SAC	School-age children
STH	Soil-transmitted helminthiasis
TAS	Transmission assessment survey
TF	Follicular trachoma
VC	Vector control
VL	Visceral leishmaniasis
WASH	Water, sanitation and hygiene
WHO	World Health Organization

Introduction

This report describes the results of mathematical modelling analyses which evaluate the impact of COVID-19-related delays or interruptions to neglected tropical diseases (NTD) programmes on the achievement of NTD goals across 7 NTDs (soil-transmitted helminthiasis; schistosomiasis; lymphatic filariasis; onchocerciasis; trachoma; visceral leishmaniasis in the Indian sub-continent and Gambiense form of human African trypanosomiasis). The findings in this report provide a quantitative framework to stakeholders who wish to understand the impact of interruption or delay of interventions on control and elimination timelines and remedial strategies that could be implemented to mitigate the delays.

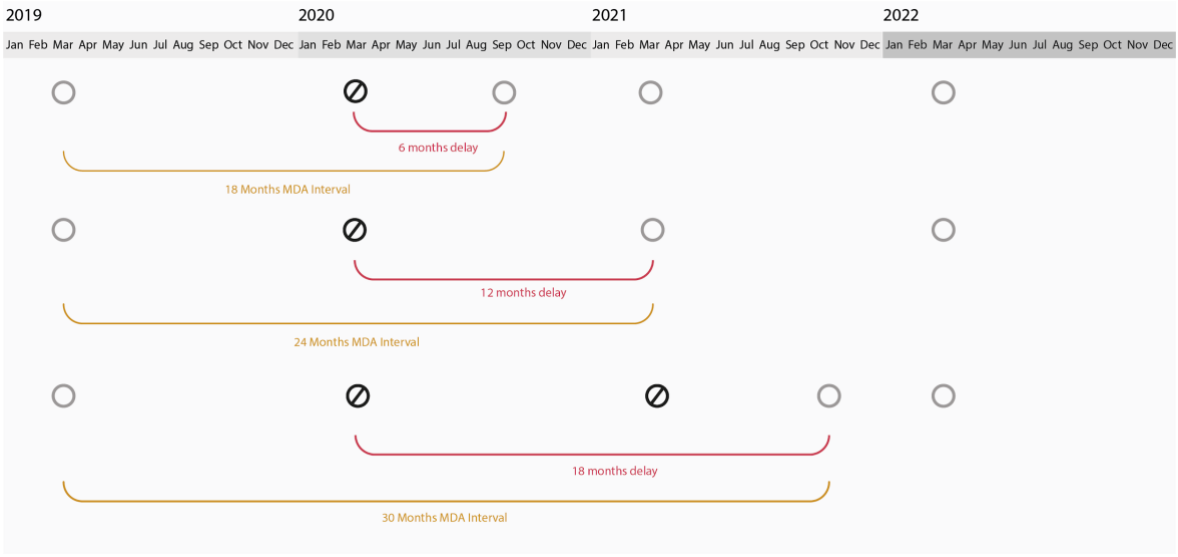
The analyses presented here are based on the transmission dynamics modelling frameworks previously developed by the NTD Modelling Consortium funded by the Bill & Melinda Gates Foundation (https://www.ntdmodelling.org/), which provide simulations under different transmission settings and a range of different intervention scenarios for each disease. The models incorporate species-specific assumptions about pathogen lifespan, vector species and dynamics, rates and heterogeneity of exposure, and pathogen distribution within human populations. Additionally, assumptions about treatment efficacy, treatment coverage, and the number of previous mass drug administration (MDA) rounds or level of screening were made for each disease.

Guide for the impact of delays in MDAs

MDAs are likely to have been delayed for a number of NTDs, with variable delays in different areas. In this report we investigate the impact of this delay on the achievement of the NTD 2030 goals and investigate different scenarios for how this impact could be mitigated.

Before the detailed results, we outline the scenarios considered, and a framework for understanding the impact of delays and mitigation strategies.

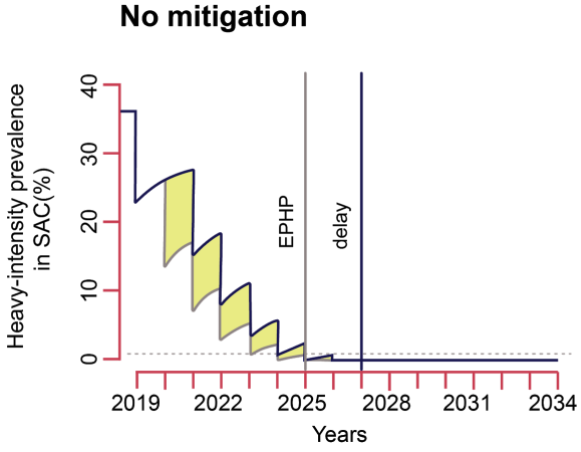
Delays and interruptions: As an example, consider a programmes in which MDAs are delivered in March every year (below, open circles), but are delayed in March 2020 (black circle crossed through). The schematic shows 6-, 12- and 18-month potential delays (in red) and resulting interval between MDA rounds (yellow).



For the majority of this report, we focus on the 12-month delay, and assume that treatments are resumed as normal in the following year. However, we also investigate results for different delays.

The impact of a delay in treatment

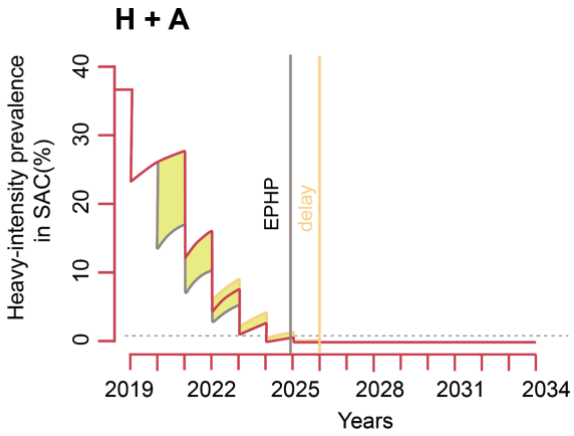
During an interruption to an MDA programmes, there will be a gradual increase in infection which would not have occurred had the MDA occurred as planned. This is illustrated below using an example from schistosomiasis. The grey line represents the prevalence of heavy infection in school-aged children (SAC) if the treatment had gone ahead as planned, and the black line shows the increase in infection prevalence due to the missed MDA.



The first vertical line shows when elimination as a public health problem would have been achieved if there had been no delay to the MDAs, and the second line shows how it is reached later as a consequence of the delay - in this case two years later. The yellow area shows the increased morbidity which occurs as result of the increased level of infection in the community.

Mitigation strategies

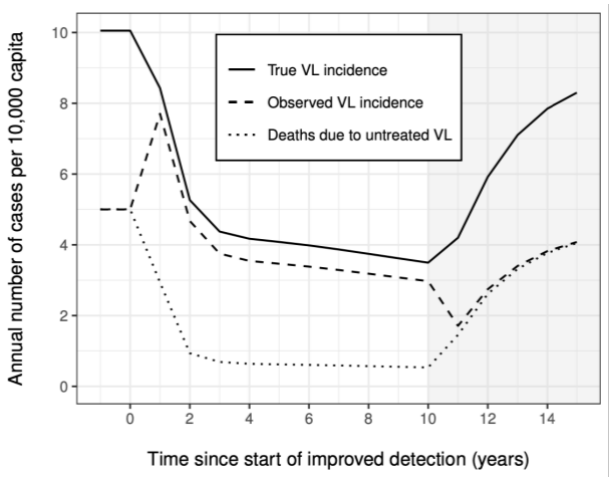
The plot below shows what would happen if higher coverage were achieved when the programmes is restarted (red line). In this case the delay to the programmes achieving its goals (yellow vertical line) is only one year, and the resulting increase in morbidity (yellow shaded area, assuming that morbidity is due to heavy-intensity prevalence) is also less.



A range of suitable mitigation strategies is explored in the disease-specific sections below, including more frequent treatments, increasing the target coverage, using different drug combinations or targeting different parts of the population.

Guide to interruptions to active case detection

In discussions with stakeholders, it became clear that there may be interruptions to active and passive case detection during the COVID-19 pandemic for visceral leishmaniasis in the Indian subcontinent and for the Gambian form of human African trypanosomiasis. Here we outline some general points about an interruption to a successful case-finding programmes using the example of visceral leishmaniasis (see graph below, adapted from Coffeng *et al*., 2019).



During a successful case-finding programme, as the programmes increases in efficacy at detecting cases we would expect to see an initial increase in cases detected (year 1 in this illustration, dashed line), while the backlog of cases is detected.

As cases start to be diagnosed earlier, we expect to see a reduction in transmission, a reduction in incidence (solid line), and a related drop in detected cases (dashed line). If, however, the programme is interrupted (grey area, year 10 onwards, in this illustration), the link between detected cases and underlying transmission is broken, and it is possible that an observed drop in detected cases could mask a resurgence in infection (year 10), or if the resurgence is detected, that it is detected late and its magnitude is underestimated (years 12 onwards).

This breaking of the relationship between detection and underlying incidence is likely to lead to a gradual increase in morbidity and mortality. The rate of increase may be slow due to the relatively slow epidemic growth rate of these NTDs, in comparison to, for example, malaria, but it is still important to quantify. The particularly concerning feature of this type of delay is that outbreaks or pockets of transmission could be missed. In the sections below, we discuss in which settings this would be more likely to occur.

Guide to the disease-specific sections of this report

The model outputs are described per disease and each section includes a description of the mathematical models used and major assumptions, a representation of the different scenarios and mitigation strategies modelled (summarized in the scheme below), graphs showing the dynamics of the prevalence of infection (for each scenario and/or mitigation strategies) as well as a table describing how the timelines to the 2030 goals are impacted.

Disease-specific analyses

Soil-transmitted helminthiasis

The 2030 goal for soil-transmitted helminthiasis (STH) is elimination as a public health problem (EPHP), defined as reaching <2% prevalence of moderate-to-high intensity infections in school-age children (SAC). Guidelines for achieving this goal recommend preventive chemotherapy (PC) in pre-SAC and SAC once per year in moderate prevalence settings (20-50% in SAC) and twice per year in high prevalence settings (>50%). Treatment of adolescent girls and women of reproductive age is also recommended (WHO, 2017). While moderate prevalence settings are likely to achieve EPHP by 2030 or earlier, high prevalence settings will require bi-annual PC, ideally including adults (Farrell *et al*., 2018). Due to Covid-19, PC for STH has been halted. As a result, the programmes will be experiencing a delay in their progress toward EPHP and some may eventually be unable to reach the EPHP goal by 2030. The impact of the delay will vary across settings. However, mitigation strategies may not be needed, as the example of the 2014 Ebola outbreak in Sierra Leone suggests (Bah *et al*., 2019). We use mathematical modelling to explore the impact of a one-year interruption of PC and the potential benefits of increased frequency/target population once the programmes resume.

Modelling approach, scenarios and mitigation strategies

We used two stochastic individual-based models developed by Erasmus MC (EMC) and Imperial College London (ICL). These models allow the simulation of the three main STH species (*Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm species) under different transmission conditions. To simulate moderate or high prevalence settings we varied the transmission conditions defined in terms of the transmission rate (EMC model)/basic reproduction number (ICL model) and the level of exposure heterogeneity, indicating how aggregated worm burdens are among hosts. Prevalence settings are defined in terms of Kato-Katz prevalence in SAC. We simulated individual villages with a population size of 500 individuals. The models assume a treatment (albendazole/mebendazole) efficacy of 94% for hookworm, 99% *A. lumbricoides* and 60% for *T. trichiura*. The effective treatment coverage was assumed to be 75% of the target population (pre-SAC and SAC or the whole community) in all years in which PC takes place. We predict the impact of the four control strategies outlined in **Figure 1** over a timeline of 10 years (2020-2030) based on 100 runs with each model.

We consider 4 different treatment scenarios (**Figure 1**) for the moderate endemicity setting and three for the high endemicity setting. *"No interruption"*, or the control scenario, implements PC as per WHO guidelines (annual or bi-annual PC). In the following scenarios, a disruption (one or two missed rounds of MDA) is simulated during the first year. *"No mitigation"* does not include any mitigation strategy while *"Bi-annual"* and *"Single community round"* increase PC frequency and target population (community-wide PC), respectively. *"Bi-annual"* scenario has

not been modelled for the high endemicity setting, as it is considered not practically feasible to conduct MDA four times per year at effective coverage.

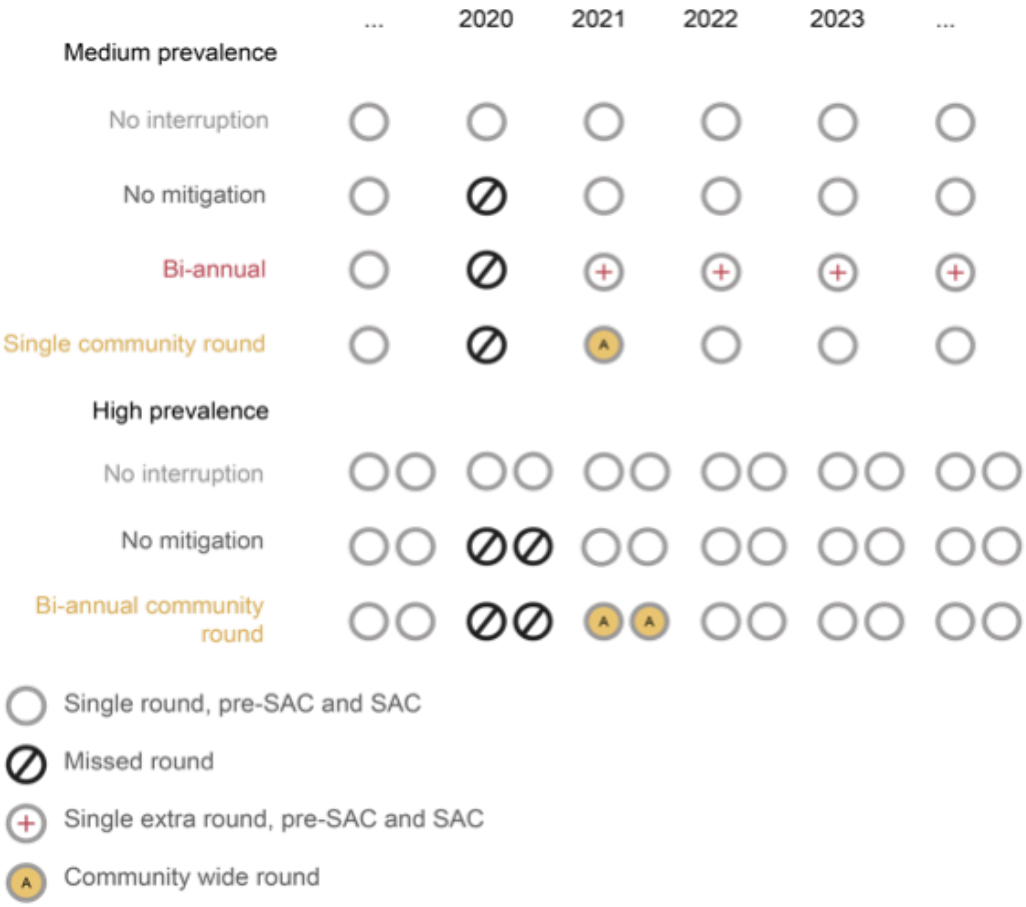


Figure 1. Visual representation of the scenarios and mitigation strategies modelled for STH.

Model outputs

Figure 2 shows the mean dynamics of the prevalence of any infection and prevalence of moderate-to-heavy infections in SAC as measured by a single slide Kato-Katz. In this figure, we present the results obtained by the EMC model as similar dynamics were observed using the ICL model. If no mitigation strategy is adopted, the programmes will catch up on their progress toward meeting the goal in less than two years for *A. lumbricoides* and hookworm (**Table 2**). *T. trichiura* may take longer to catch up. A round of community-wide MDA when programmes resumes would be sufficient to compensate for the year missed in both hookworm and *A. lumbricoides*. Bi-annual PC will further reduce the time to EPHP by 1.5 years on average. As anticipated by previous modelling work (Coffeng *et al*., 2015, Farrell *et al*., 2018) the high prevalence settings are unlikely to meet the EPHP target by 2030 but mitigation strategies to make up for the skipped MDA round(s) will still be beneficial.

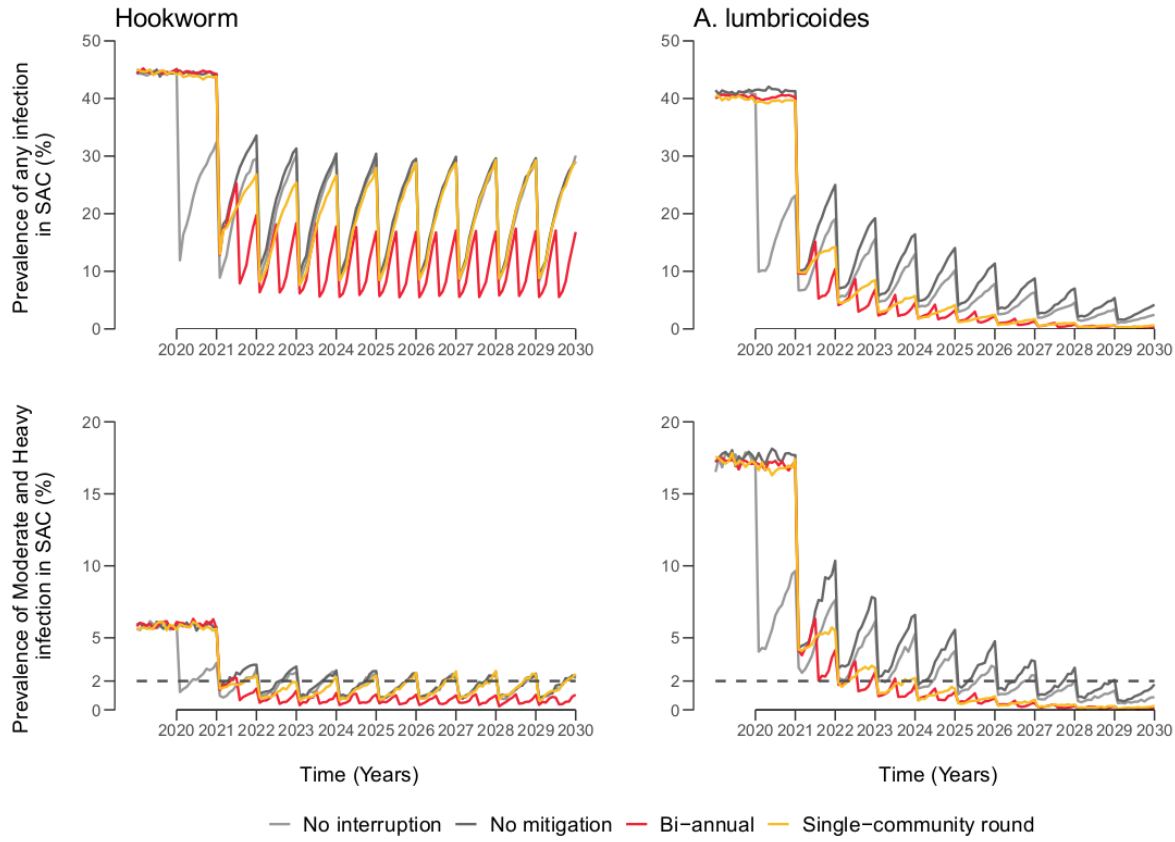


Figure 2. Mean dynamics of the prevalence of any infection and prevalence of moderate-to-heavy infections in SAC as measured by a single slide Kato-Katz (moderate setting). Only results from the EMC model are shown.

Table 2. Delay in years to reach the same moderate-heavy prevalence in SAC (progress towards EPHP) if a year of MDA is missed and no mitigation strategy is implemented ("*No mitigation*" scenario) as compared to the "*No interruption"* scenario

Species	Model	Moderate Prevalence (20-50%)	High Prevalence (>50%)
A. lumbricoides	ICL	1.49 (1 - 3)	1.66 (1 - 3.5)
	EMC	1.69 (1 - 4)	1.49 (1 - 2)
Hookworm	ICL	1.23 (1 - 2)	1.23 (1 - 1.5)
	EMC	1.41 (1 - 2)	1.30 (1 - 2)
T. trichiura	ICL	1.77 (1 - 7)	1.92 (1 - 6.5)
	EMC	2 (1 - 6.5)	2.4 (1 - 7)

Summary

- A round of community-wide MDA when programmes resume is sufficient to compensate for the year missed for hookworm and *A. lumbricoides*.
- High prevalence settings are unlikely to meet the EPHP target by 2030 but mitigation strategies to make up for the skipped MDA round(s) will still be beneficial.
- If no mitigation strategy is adopted, the programmes will catch up on their progress toward meeting the goal in less than two years for *A. lumbricoides* and hookworm. *T. trichiura* may take longer to catch-up.

Further details

The two models are based on similar biological and demographic assumptions. Worm death, as infection, is a stochastic process depending on the mean species-specific worm lifespan. Both models include age-structured host populations with birth and death rates typical for low- and middle-income countries (LMICs_. Individual hosts acquire STH infection via contact with an environmental reservoir (eggs, larvae). Exposure and contribution to the infectious environmental reservoir (i.e. practice of open defecation) are age-specific but differ in the functional forms and parameterization between the models and for different STH species. Limitations of the models include that the parameters quantifying exposure heterogeneity were fitted on data from high prevalence settings for *T. trichiura* and *A. lumbricoides*. Evidence from field studies suggests that exposure heterogeneity could be higher for lower prevalence settings (Truscott *et al.*, 2019). Moreover, for the sake of simplicity the analyses presented here do not consider systematic non-access to treatment. Full details about EMC model structure and parameterization have been published previously (Coffeng *et al*., 2015; Coffeng *et al*., 2017). The individual-based ICL model has been presented in previous studies (Farrell *et al*., 2017; Farrell et al. 2018) and described in its deterministic version in earlier work (e.g. Truscott *et al.*, 2014).

Schistosomiasis (*Schistosoma mansoni*)

The 2030 goal for schistosomiasis is elimination as a public health problem (EPHP), achieved when the heavy-intensity prevalence in school-age children (SAC; 5-14-year old) is reduced to less than 1% (WHO, 2011). Mass drug administration (MDA) of praziquantel is the main tool for control with a focus on the treatment of SAC. For high prevalence settings, the treatment of adults (≥15-year old) considered to be at risk of infection is also recommended (WHO, 2006). However, due to COVID-19, many mass treatment campaigns for schistosomiasis have been halted (WHO, 2020). As a result of MDA being postponed, the programme will be at risk of not reaching the EPHP goal by 2030. The impact of the delay and the appropriate mitigation strategy are likely to vary across different programmatic settings.

Also, it should be noted that certain high prevalence settings will not be on track for reaching EPHP by 2030, regardless of halting MDA, unless both SAC and adults are being treated at the appropriate coverage levels (Toor *et al*., 2019, Kura *et al*., 2019).

Modelling approach, scenarios and mitigation strategies

In our investigation, we considered a moderate (30% baseline prevalence among SAC) and a high (70% baseline prevalence among SAC) prevalence settings prior to MDA. In addition to this, we used two different age intensity profiles (low and high burden of infection in adults) to determine whether this would differentially influence the impact of missing MDA rounds. In the model, we implemented MDA annually at a 75% coverage level of SAC only. We then missed one MDA round either early or late (second or sixth round of MDA, respectively) into the programmes. For all of our scenarios, we determined the time taken to achieve EPHP. After a missed round of MDA, we considered three mitigation strategies (**Figure 3**): (i) return with annual 75% coverage level of SAC-only, (ii) return with annual 85% coverage level of SAC only and (iii) return with one-year community-wide coverage (85% SAC + 40% adults) followed by 75% coverage of SAC-only in the years following this.

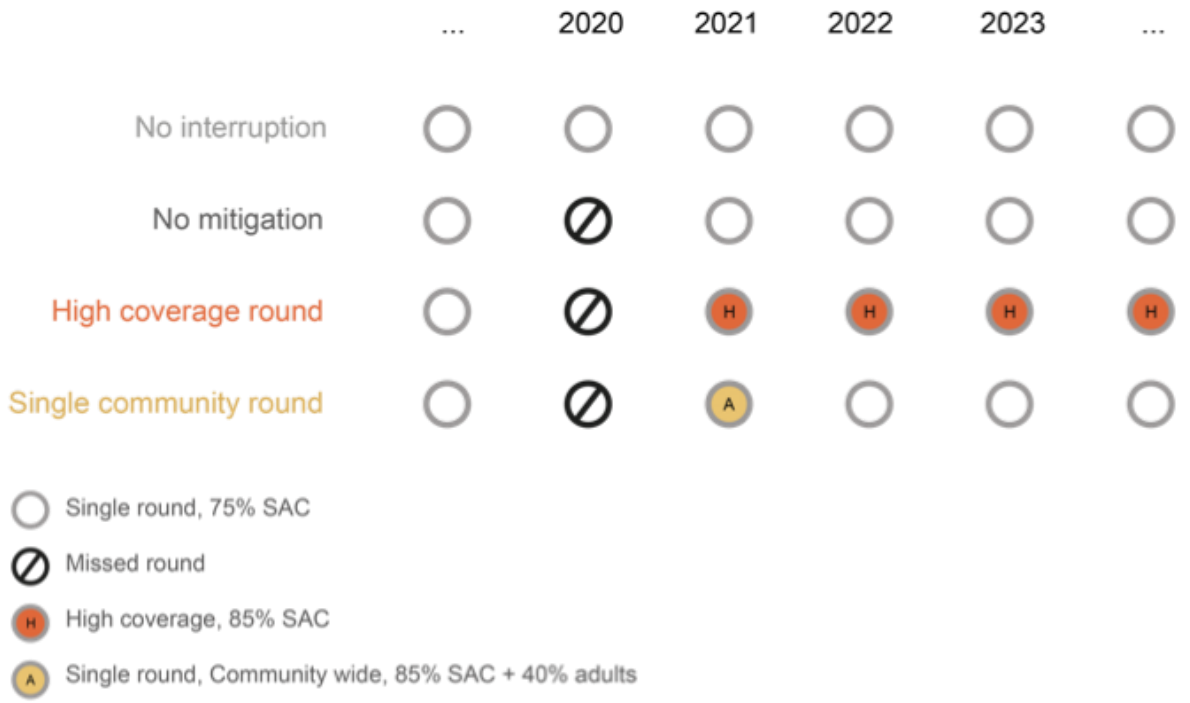


Figure 3: Visual representation of the scenarios and mitigation strategies modelled for schistosomiasis.

We adopt a deterministic model developed by Imperial College London (ICL) (Anderson *et al*., 2016). The model incorporates treatment by MDA and is parameterised for *Schistosoma mansoni* with previously published data/values matching with past epidemiological studies (Toor *et al*., 2018). For each transmission setting and age profile (**Figure 4**), we simulate the impact of different control strategies (as described above) over a period of 15 years. For each point in time, we determine the prevalence of heavy-intensity infections (eggs per gram, epg ≥ 400) in SAC to investigate whether the EPHP goal has been achieved.

Although *S. haematobium* was not modelled in this investigation, as this species typically has a low burden of infection in adults, the results are likely to be similar to *S. mansoni* with a low burden of infection in adults.

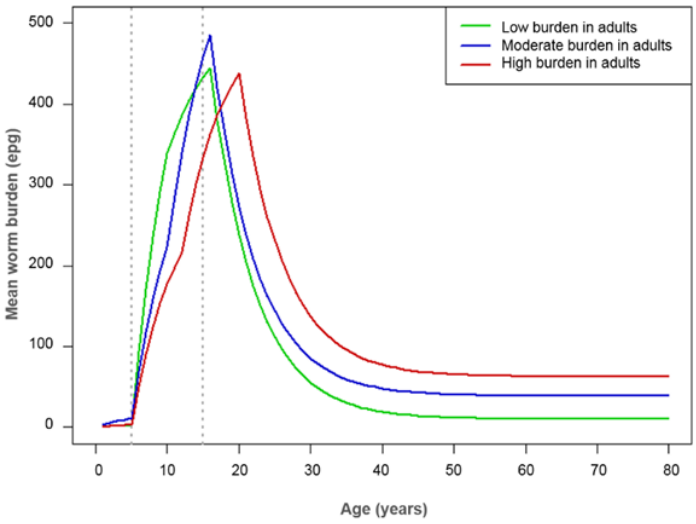


Figure 4: *Schistosoma mansoni* age-intensity profiles of infection showing low, moderate, and high burden of adult infection settings (Toor *et al*., 2018).

Model outputs

For the moderate transmission setting with a low infection burden in adults, missing the second round of MDA (**Table 3**), requires an additional year of intervention to achieve EPHP, regardless of the mitigation strategy. This is due to the fact that we are skipping the second round of treatment, which is the round when EPHP is achieved under normal circumstances (no interruption of MDA). Similarly, a one-year delay is also expected for high adult burden when the programme is reintroduced at the previous coverage (**Table 3**). However, increasing the coverage level to 85% (or having one round of community-wide MDA) does not require the additional year of intervention. Missing the sixth round of MDA does not have any impact on the time required to achieve the EPHP goal (**Table 4**).

For the high transmission setting with a low infection burden in adults, if the programme is reintroduced at the previous 75% SAC-only coverage, then we would expect two years of delay in reaching EPHP (**Tables 3**, **4** and **Figure 5**), regardless of the time MDA is missed. Increasing coverage level to 85% of SAC, does not require the additional two years if the second round of MDA is missed.

For the high transmission setting with a high adult burden, EPHP is not achieved by 2030 regardless of the mitigation strategy **(Tables 3, 4** and **Figure 6)**. This is because MDA of SAC only is having a small impact on reducing transmission. To achieve EPHP within a shorter time frame, higher coverage of SAC and adults would be needed for this setting (Toor *et al*., 2019).

In summary, missing MDA results in a delay of up to two years for achieving EPHP. The impact of missing MDA for one year depends on the baseline prevalence prior to treatment, the burden of infection in adults and the time at which MDA is missed (early or late into the programmes).

Table 3: Years of MDA to achieve EPHP (≤1% heavy-intensity prevalence in SAC) for *S. mansoni*. The second round of MDA is missed. NA: not achievable by 2030. Results are shown for low and high adult burden of infection settings using the Imperial College London deterministic model. (NA: not achievable)

Prevalence in SAC	**Moderate** (30%)	**High** (70%)
Time to EPHP if no postponement to annual 75% SAC MDA	Low-high adult burden setting: 2 - 3 years	Low-high adult burden setting: 7 - NA years
Delay to EPHP if 2nd MDA missed + return with 75% SAC	Low-high adult burden setting: 1 year	Low-high adult burden setting: 2 - NA years
Delay to EPHP if 2nd MDA missed + return with 85% SAC	Low-high adult burden setting: 1 - 0 years	Low-high adult burden setting: 0 - NA years
Delay to EPHP if 2nd MDA missed + return with 1 community-wide MDA (85% SAC + 40% adults) followed by 75% SAC	Low-high adult burden setting: 1 - 0 years	Low-high adult burden setting: 1 - NA years

Table 4: Years of MDA to achieve EPHP (≤1% heavy-intensity prevalence in SAC) for *S. mansoni*. The sixth round of MDA is missed. NA: not achievable by 2030. Results are shown for low and high adult burden of infection settings using the Imperial College London deterministic model. (NA: not achievable)

Prevalence in SAC	**Moderate** (30%)	**High** (70%)
Time to EPHP if no postponement to annual 75% SAC MDA	Low-high adult burden setting: 2 - 3 years	Low-high adult burden setting: 7 - NA years
Delay to EPHP if 6th MDA missed + return with 75% SAC	Low-high adult burden setting: 0 years	Low-high adult burden setting: 2 - NA years
Delay to EPHP if 6th MDA missed + return with 85% SAC	Low-high adult burden setting: 0 years	Low-high adult burden setting: 2- NA years
Delay to EPHP if 6th MDA missed + return with 1 community-wide MDA (85% SAC + 40% adults) followed by 75% SAC	Low-high adult burden setting: 0 years	Low-high adult burden setting: 2 - NA years

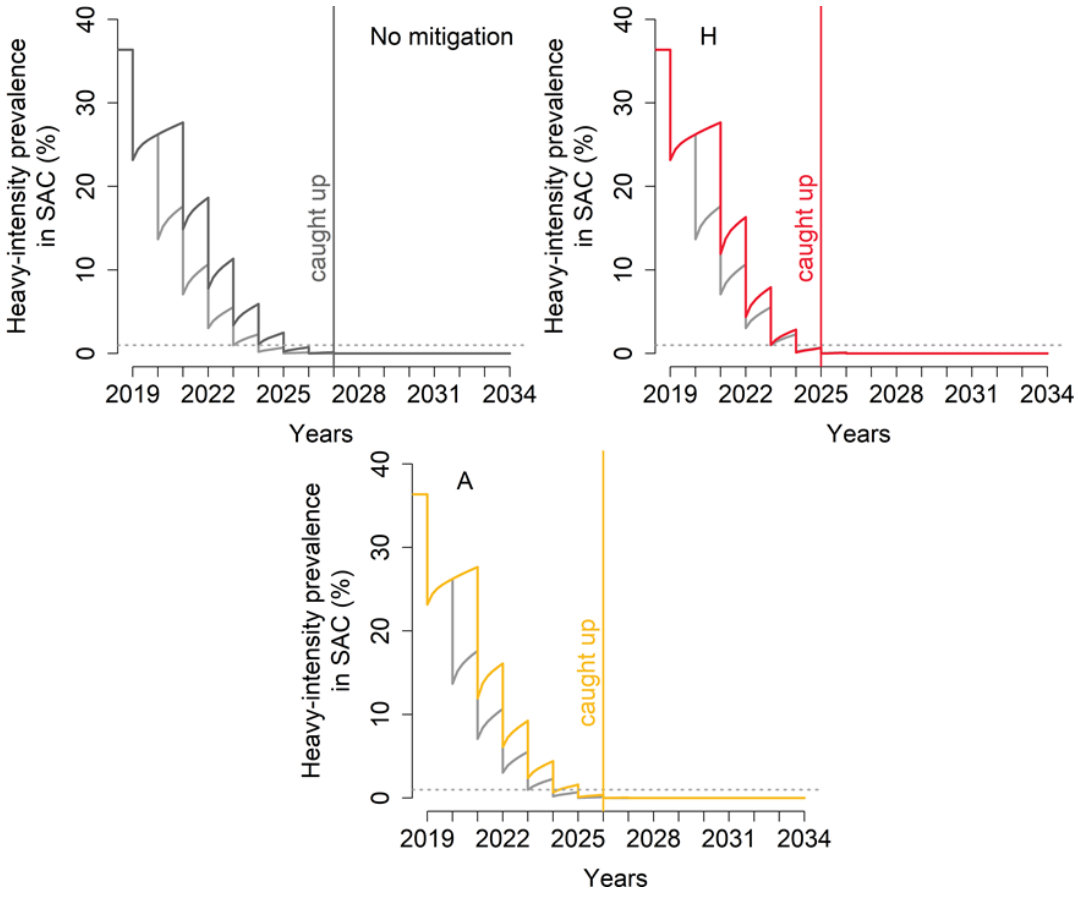


Figure 5: Heavy-intensity prevalence in SAC in high transmission settings with a low adult burden of infection. The second round of MDA is missed. (**No mitigation**) the programme is restarted by treating 75% of SAC. (**H**) the programme is restarted by treating 85% of SAC. (**A**) the programme is restarted with 1 community-wide MDA (85% SAC + 40% adults) followed by 75% SAC.

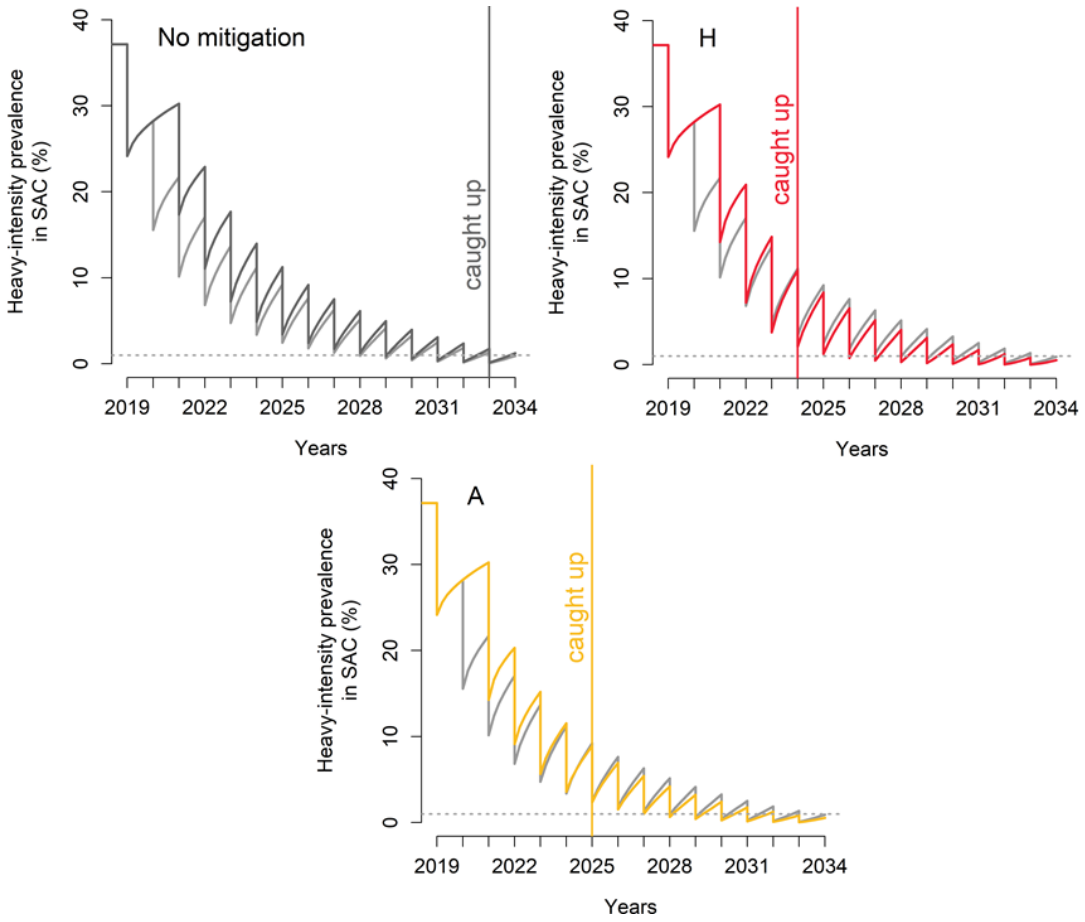


Figure 6: Heavy-intensity prevalence in SAC in high transmission settings with a high adult burden of infection. The second round of MDA is missed. (**No mitigation**) the programme is restarted by treating 75% of SAC. (**H**) the programme is restarted by treating 85% of SAC. (**A**) the programme is restarted with 1 community-wide MDA (85% SAC + 40% adults) followed by 75% SAC.

Summary

- Postponing MDA results in the EPHP goal being delayed by up to two years.
- In high prevalence settings, EPHP may not be achieved by 2030 regardless of a postponement, unless treatment of adults is included in the MDA programme.
- Postponement of MDA may have a lower impact in higher adult burden settings as here MDA of SAC-only is having a smaller impact on reducing transmission.

Further details

The ICL model is an age-structured deterministic model which describes the dynamics of the adult worms in the human host population and a single reservoir of infectious material (short-lived infected snails) (Anderson & May 1985). This model assumes a negative binomial distribution of parasites per host with a fixed aggregation parameter, density-dependent female worm fecundity, and assumed monogamous sexual reproduction among worms.

The egg contribution to the reservoir depends on the age-specific contact rate for each individual in the population.

The simulations were run for a single community with a population size set at 1000, with no effect of migration. In our simulations, treatment is delivered at random at each round i.e. no systematic non-adherers and no non-access individuals. Acquired protective immunity is not taken into consideration. To simulate moderate and high baseline prevalence settings (for low and high adult burden of infection), the intrinsic intensity of transmission, i.e. basic reproductive number (R_0), was varied (higher prevalence settings corresponding to higher R_0 values). For each control strategy, we assumed that praziquantel has an efficacy of 86.3% (Zwang & Olliaro, 2014).

Note: An individual-based stochastic model under development by the University of Oxford was also investigated but is undergoing further development.

Lymphatic filariasis

The 2030 goal for lymphatic filariasis (LF) is elimination as a public health problem (EPHP), which is in part validated by passing defined transmission assessment surveys (TAS). Annual mass drug administration (MDA) for a minimum of 5 years, with at least 65% coverage, is the main recommended tool for achieving EPHP. Combinations of ivermectin and albendazole (IA, in Africa where onchocerciasis may co-occur) or DEC and albendazole (DA, elsewhere without onchocerciasis) are most commonly used in MDA programmes, but recent studies have shown a triple-drug combination (IDA) can substantially improve results in foci without onchocerciasis (Irvine *et al.*, 2017, Michael *et al.*, 2017, Stolk, *et al.*, 2018), but this can only be used in a limited number of areas due to risks of adverse events.

In previous occasions where MDA has been interrupted, it has been possible to come back the following year with good coverage. In Haiti, following the 2010 earthquake, there was 92% reported coverage of MDA for LF in 2011 (Streit *et al.*, 2013). Similarly, Sierra Leone and Liberia missed MDA in 2014 due to the West Africa Ebola epidemic (Mupfasoni *et al.*, 2016), but both countries managed to resume MDA in 2015 and reported >70% coverage (WHO, 2015; Liberia MoH, 2016). However, whilst Guinea achieved 16% coverage during the outbreak, this only increased to 21% in 2015; although by 2016 coverage was up to 73% (WHO, 2016). Unfortunately, there is little information available on how these interruptions affected programme outcomes, as the majority of districts are still undertaking MDA, but by 2019, 9 of 14 endemic districts in Sierra Leone had stopped MDA (Helen Keller International, 2019).

Modelling approach, scenarios and mitigation strategies

Three mathematical models for LF have been developed by members of the NTD Modelling Consortium (EPIFIL, LYMFASIM and TRANSFIL), which have been recently used to inform policy questions (Michael *et al.,* 2018, Stolk, Prada *et al.* 2018, Prada, Davis *et al.* 2019). To illustrate the impact of COVID-19 on LF programme we use below results from TRANSFIL, a

stochastic individual-based model simulating worm burden and microfilaraemia; results were qualitatively similar across all three models and different drug combinations (IA and DA).

We focus our analysis on bancroftian filariasis transmitted by *Anopheles* vectors (mostly rural Africa), assuming 30% bed-net coverage and IA usage. We consider strategies for mitigating a one-year disruption, **Figure 7**. Mitigation timelines for locations using DA are similar, but using IDA is also possible. We also simulated extending these strategies to accelerate goal achievement.
To generate a range of prevalences we vary three parameters: vector to host ratio, population bite risk and importation rate. Parameters are based on previous analyses (Irvine *et al.*, 2015, 2017) and the population size considered is typical of rural African communities: most are small (~1500), but a handful are large (max = 12000). We then simulate each MDA strategy outlined in **Figure 7**, considering systematic non-adherence and drug efficacy (Prada, Davis *et al*., 2019).

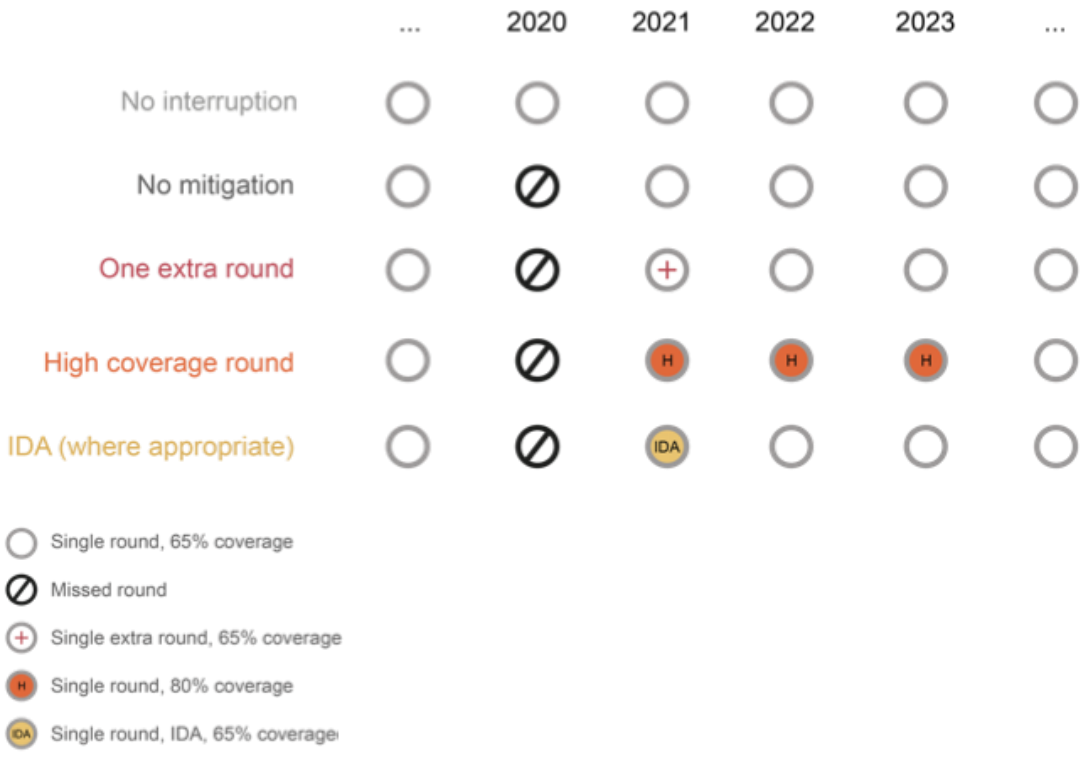


Figure 7: Catch up methods after missing one year of MDA for LF. Dark grey: resume at 65% coverage. Red: one year of bi-annual MDA after the programme restarts. Orange: three years increased coverage (80%) then resume 65%. Yellow: resume the programmes with one round IDA, then return to the previous regime (in areas using DA).

Model outputs

Table 5 shows the expected number of years we predict IA programme would be delayed in achieving 1% microfilarial (mf) prevalence due to 1-2 missed rounds of MDA, assuming the programme resumes at 65% coverage until reaching the 1% target. Mean delay is less than the interruption length in all prevalence settings, but the variation is likely to be higher in high endemicity locations, with up to 3 years of delay possible from one missed round. In low endemicity settings (5-10% mf prevalence), if programmes have already started by 2018 then any delay would not be expected to impact the achievement of the 2030 goal.

Table 5: Delay to achieving 1% mf prevalence goal, years (95%CI), if one or two MDAs are missed, plus expected time to the goal (from 2018) if no interruption. Timeframes >12 years won't reach the goal by 2030

Prevalence setting (2018)	Low (5-10%)	Medium (15-20%)	High (25-30%)
Time to the goal if no interruption	7.38 years (5-11)	10.25 years (7-16)	12.03 years (9-16)
Delay to the goal if 1 MDA missed	0.65 years (0-2)	0.61 years (0-3)	0.61 years (0-3)
Delay if 2 MDAs missed	1.31 years (0-3)	1.24 years (0-3)	1.15 years (0-4)

When considering which mitigation strategy is better to 'catch-up' a missed year due to disruption such as the COVID-19 outbreak, bi-annual MDA or switching to IDA are the most efficient (although the use of IDA is only possible in areas currently using DA for the reasons described above). Both lead to catching up 1 year after the programme resumes, whereas enhancing coverage to 80% takes three rounds (see **Figure 8** for example 15% mf prevalence in 2018). This is most relevant in high prevalence settings, where countries are not expected to achieve the goals by 2030 without mitigation strategies.

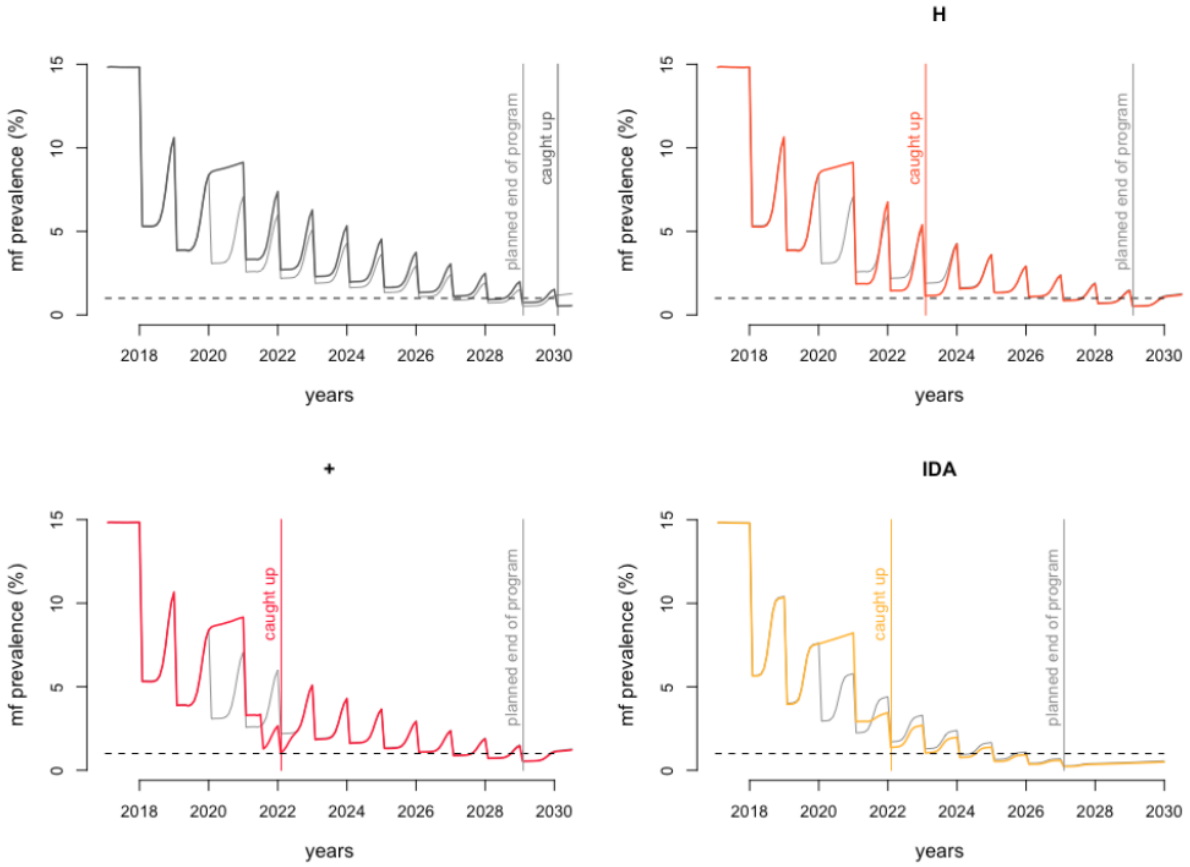


Figure 8: Example for 15% mf prevalence (2018) with IA (DA lower right). Assuming one round of missed MDA in 2020 and using catch up methods from Figure 4 (continue at 65%, dark grey; 3 rounds 80%, orange; 1 round biannual MDA in year 5, red; 1 round IDA in year 4, yellow). The dashed line shows 1% mf prevalence.

Resuming at previous coverage levels will necessitate an additional round of MDA in most cases, extending the programmes by a year. In comparison, enhancing coverage to 80% for three years would amount to the equivalent of one 45% coverage round of medication, reducing the drug resources required as well as programme duration. One round of bi-annual MDA would use the same number of treatments as extending the programme by a year. One round of IDA would require 65% coverage of ivermectin (I). However, programmes logistical costs are also likely to be impacted.

Although the impact of a short interruption to MDA distribution is likely to be small in most cases, settings that are behind schedule (>25% prevalence in 2018) could use this as an opportunity to accelerate progress towards the 2030 goals by sustaining any of these catch-up strategies beyond the minimum recommended duration mentioned above after the programme resume. By simulating the continuation of these strategies, we can consider how this impacts programme duration, and hence achievement of the 2030 goals (**Figure 9**). We see that increasing coverage has the smallest impact on time to reach 1% mf prevalence, but both biannual MDA and switching to IDA (where possible) give large differences of up to 3-4 years in programme length.

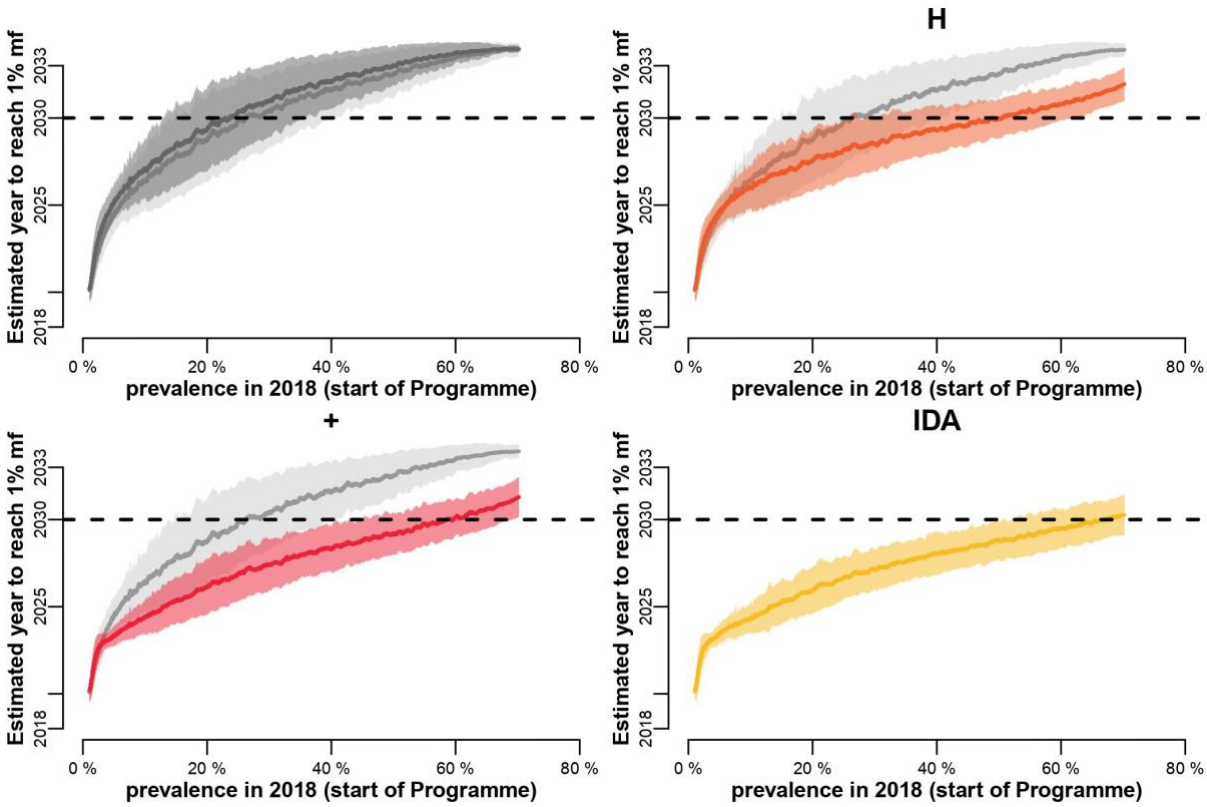


Figure 9: Sustained acceleration methods after 1-year MDA interruption in 2020. Black: reference (i.e. no rounds missed with IA); Grey: 65% coverage; Orange: 80% coverage; Red: 65% biannual; Yellow: 65% IDA (DA settings only). standard deviations are shown as the shaded regions.

Summary

- Without enhanced interventions, the mean delay is (on average) less than the number of missed rounds.
- Programmes with higher prevalence may see less delay due to more rounds still to complete. However, variation around this delay may be larger (some delays could be up to 3 years).
- Interruption is most important in places expected to reach the goal in exactly 2030.

Further details

The models have been described elsewhere and have been applied to support decision making on control and elimination of LF (Michael *et al.,* 2018, Stolk, Prada *et al.,* 2018, Prada, Davis *et al.,* 2019). They capture the basic processes relevant to LF transmission, such as vector density and biting rate, parasite life cycle, and human exposure to vectors. A small importation rate is used in the stochastic models to allow maintenance of low-level prevalence but is reduced proportionally to the expected prevalence reduction to ensure it doesn't dominate the dynamics. Moreover, adherence between rounds is modelled based on Griffin *et al.* (2010), where a parameter is used to model the probability of an individual making the same decision in sequential rounds of treatment (see Dyson *et al.,* 2017 for more details).

Here we assume that this parameter is equal to 0.35. Several questions also remain open surrounding the efficacy and safety of IDA, particularly the use of DEC is not currently safe in areas using IA (as DEC is not safe in areas where onchocerciasis also occurs). In this study, and in line with previous work (see Stolk, Prada *et al.,* 2018), we assume that microfilarial clearance by IDA is 100%, and that IDA has the same macrofilaricidal properties as DA (55%), but remaining worms are sterilised permanently (Thomsen *et al.,* 2016).

Onchocerciasis

The WHO target for onchocerciasis is the elimination of transmission (EOT), so a set mf prevalence target is not applicable; the analysis therefore focuses on trends of mf prevalence dynamics and elimination probabilities. Country-wide EOT is thought to be achievable by 2030 in 12 countries; other countries are expected to achieve this in one or more foci within the country. The main strategy towards this goal is annual ivermectin MDA; in some countries or subnational areas, biannual MDA is provided and/or complemented by vector control to accelerate EOT. The current COVID-19 pandemic will likely lead to a temporary interruption of MDA programmes. Although temporary interruptions of interventions have taken place in some countries, e.g. due to civil unrest or the Ebola epidemic in 2014, the epidemiological implications of such interruption are not well known. We use mathematical modelling to explore how a one- or two-year interruption of MDA affects infection prevalence and elimination prospects in African countries.

Modelling approach, scenarios and mitigation strategies

Two available onchocerciasis transmission models (EPIONCHO-IBM (Hamley, Milton *et al*., 2019) and ONCHOSIM (Stolk, Walker *et al*., 2015)) are used to simulate the effect of a 1- or 2-year interruption in annual MDA on the infection (microfilarial) prevalence trends. Scenarios and mitigation strategies are modelled for African settings with annual MDA since 2006 (long history of control) or since 2014 (short history of control), across a range of baseline prevalence values. Simulated scenarios for 2020 and beyond are shown in **Figure 10**.

For each of the 7 scenarios outlined in **Figure 10**, we performed simulations for pre-control prevalence levels ranging from 20%-85%, i.e., from hypo- to holoendemicity (100 simulations per 1% prevalence bin) with each model, and present the mean dynamics for microfilarial prevalence (**Figure 11**), and the probabilities of elimination (**Figure 12**). Key transmission parameters (vector biting rate - both models - variation in exposure to vector bites between individuals in the population - both models - density-dependent adult worm parasite establishment - EPIONCHO-IBM - and parasite importation rate - ONCHOSIM) are varied between simulations so that the pre-control microfilarial prevalence among individuals aged ≥5 years ranges between 20% and 85%. The population size was fixed at 440 (small rural settings). Coverage and systematic non-adherence to treatment are fixed at 65% and 5% (both models), excepting during the one or two years of remedial increased coverage (set at 80%).

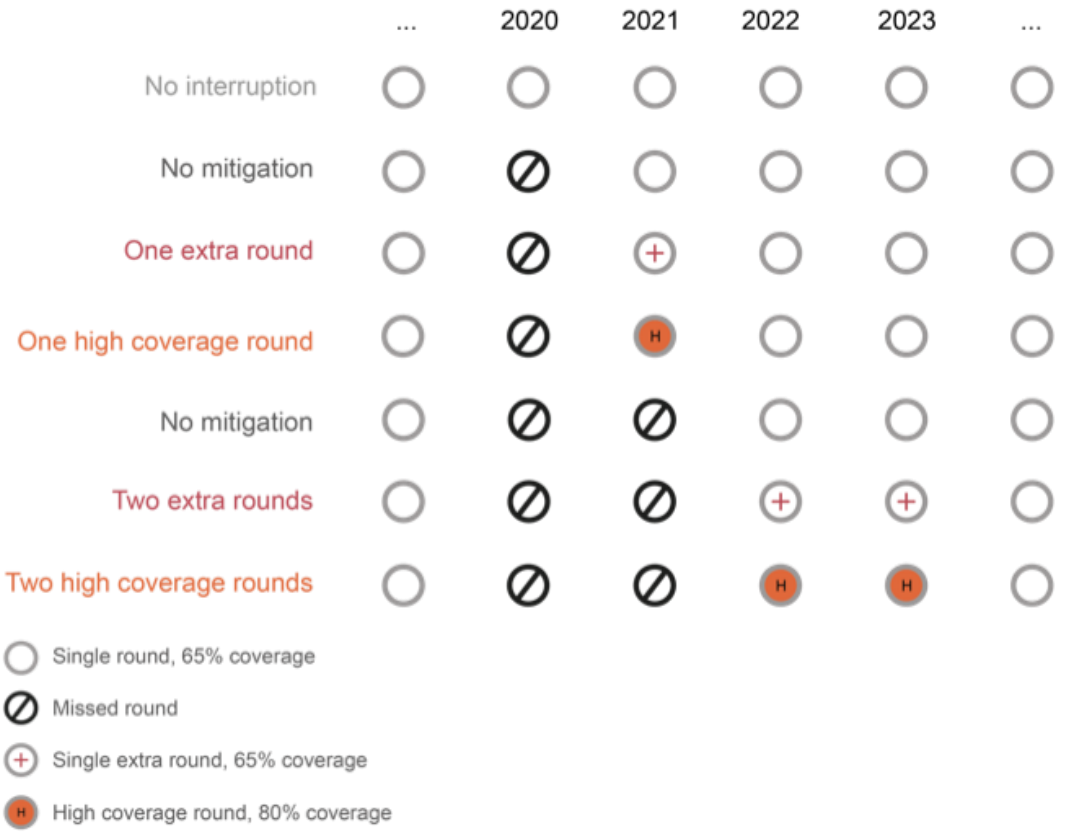


Figure 10. Scenarios simulated to understand the impact on onchocerciasis of missing 1 or 2 years of ivermectin MDA, and the mitigation effect of taking remedial action in the 1 or 2 years following the interruption. All scenarios are simulated for settings with a long history (starting in 2006) or a short history (starting in 2014) of annual MDA for a wide range of baseline prevalence values.

Model outputs

Figure 11(a) (EPIONCHO-IBM) and **11(b)** (ONCHOSIM) show, for a 50% baseline microfilarial prevalence and annual MDA starting in 2014 (65% coverage), the effect on (mean) microfilarial prevalence of missing one round (2020, dashed dark grey) or two rounds (2020 and 2021, solid dark grey), in comparison with no interruption of treatment (light grey), if no remedial strategies are implemented in the years following the interruption. Whilst for EPIONCHO-IBM the increase in prevalence is substantial, ONCHOSIM predicts less of an increase, suggesting that the parasite

population may be declining. (Ivermectin is considered not macrofilaricidal, so microfilarial dynamics are important.) **Figure 11(c)** and **11(d)** show, the effect of missing two annual treatment rounds (2020 and 2021) and the impact of either increasing the annual treatment coverage to 80% (orange) or increasing the frequency to biannual (red) with the same coverage (65%) during the two years following the interruption, after which programmes resume the strategy pursued before the interruption of MDA.

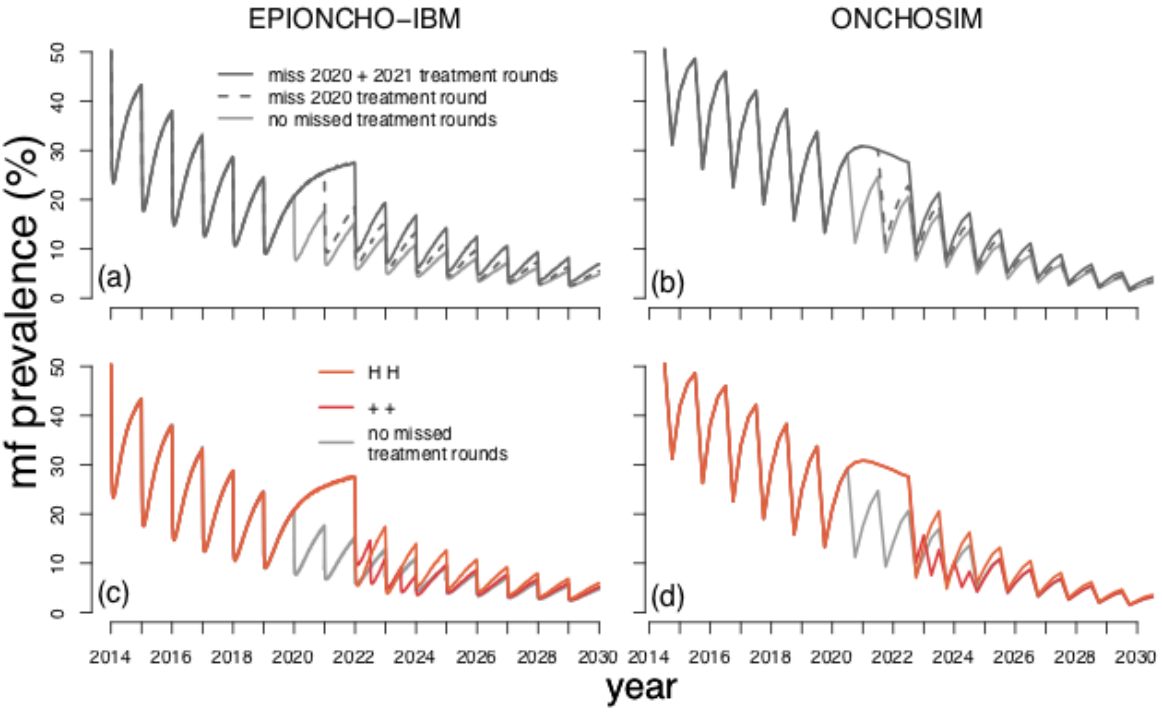


Figure 11: Mean microfilarial (mf) prevalence dynamics during ivermectin MDA predicted by EPIONCHO-IBM (a) and (c), and ONCHOSIM (b) and (d).

Figure 12 shows that although EPIONCHO-IBM (a) and ONCHOSIM (b) differ considerably in their predictions regarding the probability of elimination for a given scenario (EPIONCHO-IBM is more resilient to interventions due to assumptions made about adult worm establishment), the qualitative differences between the scenarios are similar (e.g. missing two years of treatment noticeably influences elimination when compared with no interruption in both models. This set back can be mitigated by implementing two years of biannual treatment, when MDA recommences).

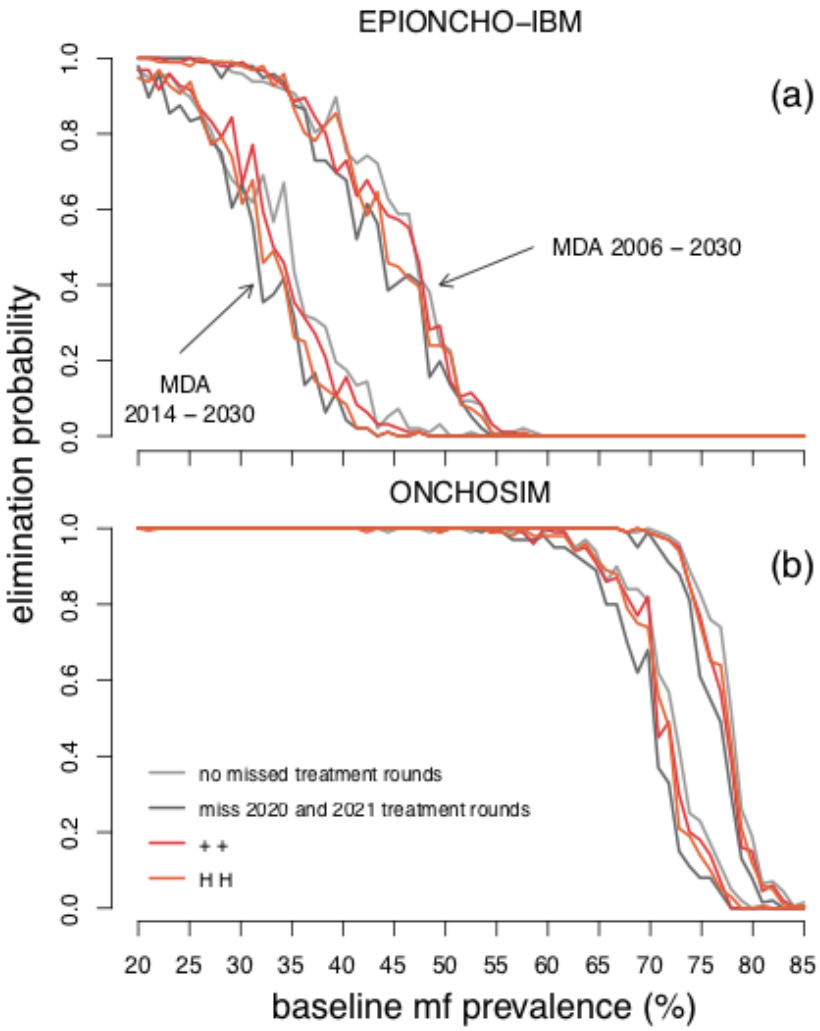


Figure 12: Elimination probabilities plotted against pre-intervention microfilarial (mf) prevalence for two treatment histories (programme starting in 2006 or in 2014) for EPIONCHO (a) and ONCHOSIM (b).

Table 6: Proportional reduction in elimination probabilities determined for 2 years interruption scenario. The reduction in elimination probability relative to that when there is no interruption in treatment (ivermectin MDA 2006-2030, 65% coverage, 5% systematic non-participation)

Baseline mf prevalence (%)		20-39 (hypoendemic)	40-59 (mesoendemic)	60-80 (hyperendemic)
No mitigation	**EPIONCHO-IBM**	Decreases by 1%	Decreases by 26%	Not achieved
	ONCHOSIM	No change	No change	Decreases by 8%
One extra round	**EPIONCHO-IBM**	No change	Decreases by 9%	Not achieved
	ONCHOSIM	no change	No change	Decreases by 4%
High coverage	**EPIONCHO-IBM**	No change	Decreases by 15%	Not achieved
	ONCHOSIM	No change	No change	Decreases by 3%

Summary

- A one-year interruption has a modest impact on elimination prospects and microfilarial prevalence.
- The impact of a two-year interruption is best mitigated by 2 years of remedial bi-annual treatment, which results in similar mf prevalence dynamics and elimination prospects to when there is no interruption.
- Remedial treatment efforts should be focused on meso- and hyperendemic areas.

Further details

The models have been described in detail elsewhere (Hamley, Milton *et al*., 2019; Stolk, Walker *et al*., 2015) and used to inform the World Health Organization 2030 targets for eliminating onchocerciasis (NTD Modelling Consortium Onchocerciasis Group 2019) and to explore the impact of various alternative/complementary strategies (Verver *et al*., 2018). Both models capture fundamental onchocerciasis population biology and transmission dynamics and are parameterised for savannah settings. The main differences between model predictions are due to the inclusion of processes regulating parasite establishment within humans (EPIONCHO-IBM)—which increases the efficiency of transmission as parasite populations decline. A small parasite importation rate (ONCHOSIM) is used to allow endemic stability of low-level prevalence.

Trachoma

The primary WHO target for elimination of trachoma as a public health problem (EPHP) is a prevalence of follicular trachoma (TF) less than 5% in children aged 1-9. Annual community-level mass drug administration (MDA) with oral azithromycin has formed the cornerstone of global trachoma control efforts, with a single dose demonstrated to have good efficacy against ocular strains of *Chlamydia trachomatis*, the causative agent for blinding trachoma (Bailey *et al*., 1993). This strategy has proved to be widely successful in community-randomized studies (Chidambaram *et al.*, 2006; House *et al*., 2009) and confirmed by the growing number of previously endemic countries which are now reaching the EPHP threshold (Lietman *et al*., 2020).

Upon disruption of MDA, empirical studies indicate that infection appears to return exponentially (Lakew *et al*., 2009; Amza *et al*., 2013) with a rate of resurgence anticipated to be faster in higher-transmission settings. In the context of programmatic activities being temporarily halted due to the global COVID-19 situation, this is especially concerning for districts mid-way through trachoma-control MDA programmes. We use model-based approaches here to explore the impact of a one-year interruption to community-level MDA and consider the potential benefits of additional catch-up rounds in the year following the resumption of activities.

Modelling approach, scenarios and mitigation strategies

The model is based on the modified SEIR framework for *C. trachomatis* transmission described by Pinsent and colleagues (Pinsent *et al.*, 2018). Of particular significance, this model structure accounts for TF persisting after clearance of *C. trachomatis,* with people transitioning through four sequential states: Susceptible (S), infected but not yet diseased (I), infected and diseased (ID) or diseased but no longer infected (D). Here disease refers to clinical trachoma, specifically TF. The original ODE model has been adapted to a fully stochastic individual-based model with age and infection/disease status of individuals explicitly incorporated (unpublished). Following the specifications of the original model, bacterial load and duration of infection and disease are assumed to decrease with each subsequent infection. Two settings are considered; Setting 1, a high transmission setting with a mean baseline prevalence of 40% in children aged 1-9 years, and Setting 2, a medium transmission setting with a mean baseline prevalence of 20% in children aged 1-9.
Each of the 4 scenarios outlined in **Figure 13** are simulated for the two settings described. The simulated interruption takes place mid-way through the programmes in each setting; Year 3 for Setting 1, and Year 2 for Setting 2. Treatment coverage for all scenarios is assumed to be 80% with an 85% efficacy of azithromycin. To simulate the potentially lower efficacy of topical tetracycline, which is routinely given to children aged less than 6 months, treatment is assumed to have an overall efficacy of 42.5% in ages 6 months and under.

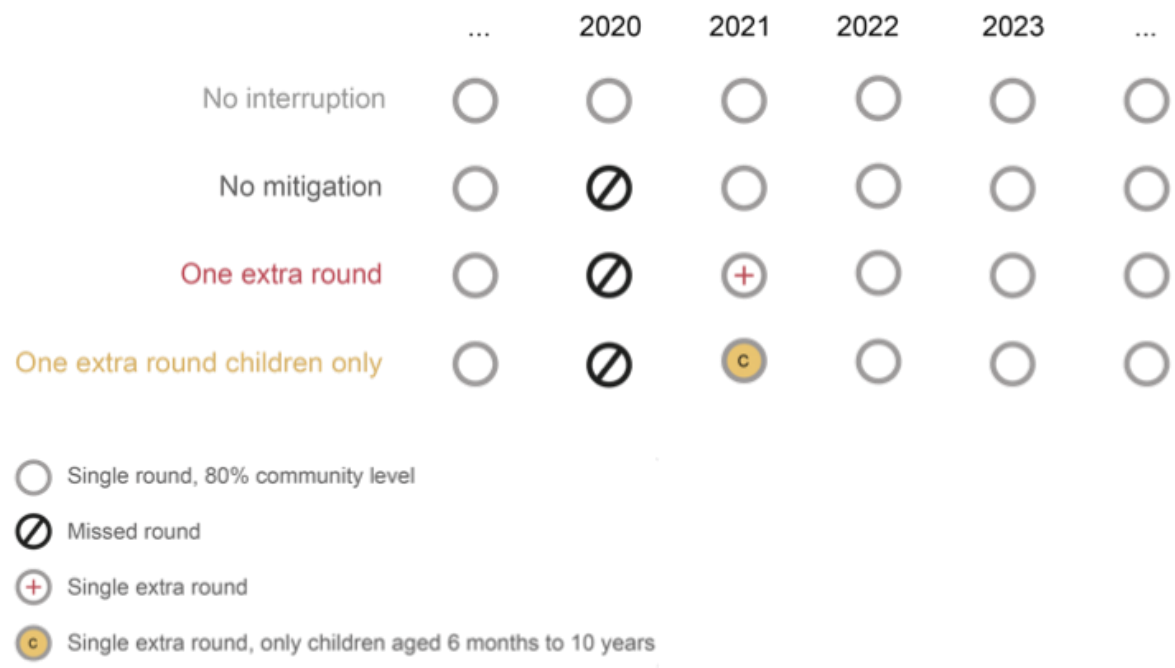


Figure 13. Schematic of the scenarios simulated in order to evaluate the impact of 1 missed year of MDA on trachoma, and the potential benefits of remedial action in the year following the interruption.

Model outputs

The time to reach the EPHP threshold, probability of reaching the threshold after 6 rounds of MDA (Setting 1) or 4 rounds of MDA (Setting 2) and the mean TF in children aged 1-9 in each setting/scenario are summarised in **Table 7**.

Figure 14 shows the TF prevalence in children aged 1-9 (TF_{1-9}) and infection prevalence in this age group in Setting 1 (high transmission) under the four different treatment scenarios outlined, with the time point when catch-up will have been achieved indicated. The delay caused by interruption to activities with no remedial action is shown clearly by the longer average time to achieve the TF_{1-9} threshold of <5% in Panel II. The impact of mitigation strategies (Scenarios "+" and "C") in the year following disruption is also shown in Figure 14, with an additional round of MDA effectively bringing the prevalence of infection back to where it would have been had disruption not occurred. It is noteworthy that this still leads to an approximately one-year delay in achieving the EPHP threshold (**Table 7**).

Figure 15 shows that for medium transmission settings, the delay in reaching the EPHP threshold is roughly equivalent to the delay in treatment (just over one year). Again, mitigation strategies with extra rounds of treatments in the year following interruption will accelerate catch-up, but given the slower bounce-back rate the additional benefit of catch-up rounds is not so pronounced, and overall, so long as the 2nd-4th rounds of MDA are delivered after the interruption, EPHP would be achieved (**Table 7**).

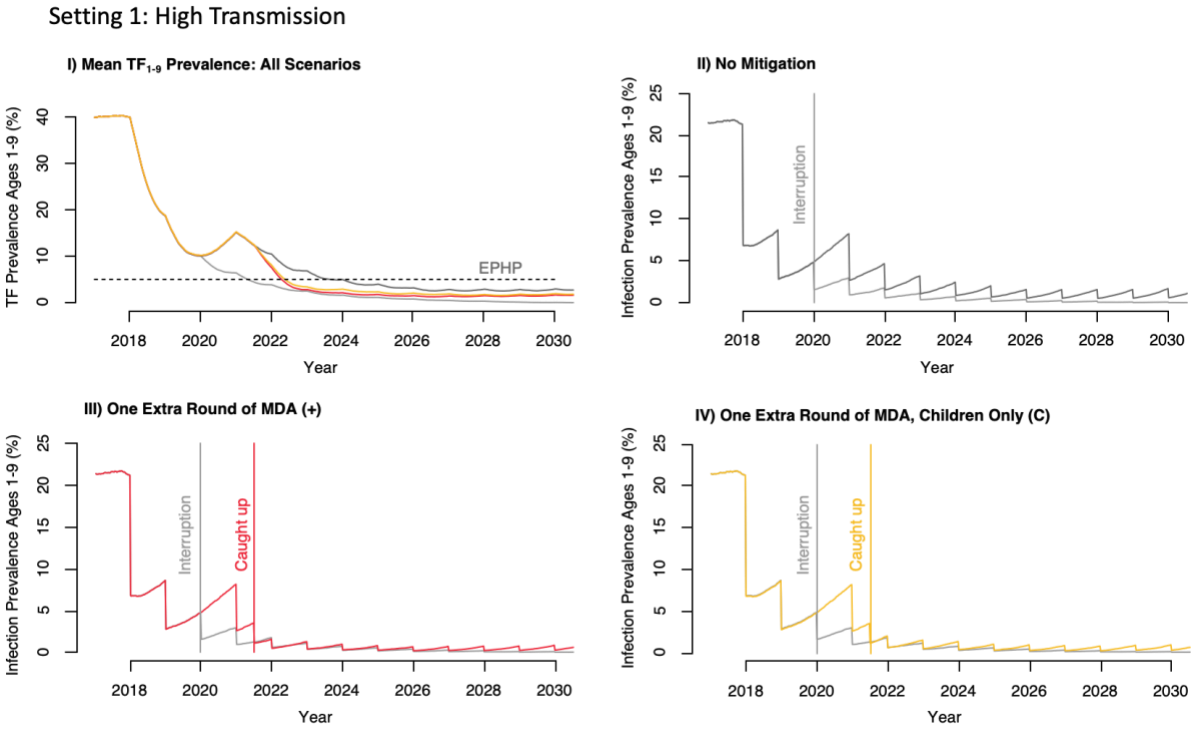


Figure 14: High transmission (Setting 1). Mean prevalence of TF in children aged 1-9 and progress towards EPHP threshold under different modelled scenarios (Panel I); Mean prevalence of trachoma infection in children aged 1-9 (Panel II-IV). Light grey represents no disruption, disruption to treatment scenarios with no mitigation is plotted as dark grey, and mitigation strategies targeting the whole community (+) and children only (C) are plotted as red and yellow respectively.

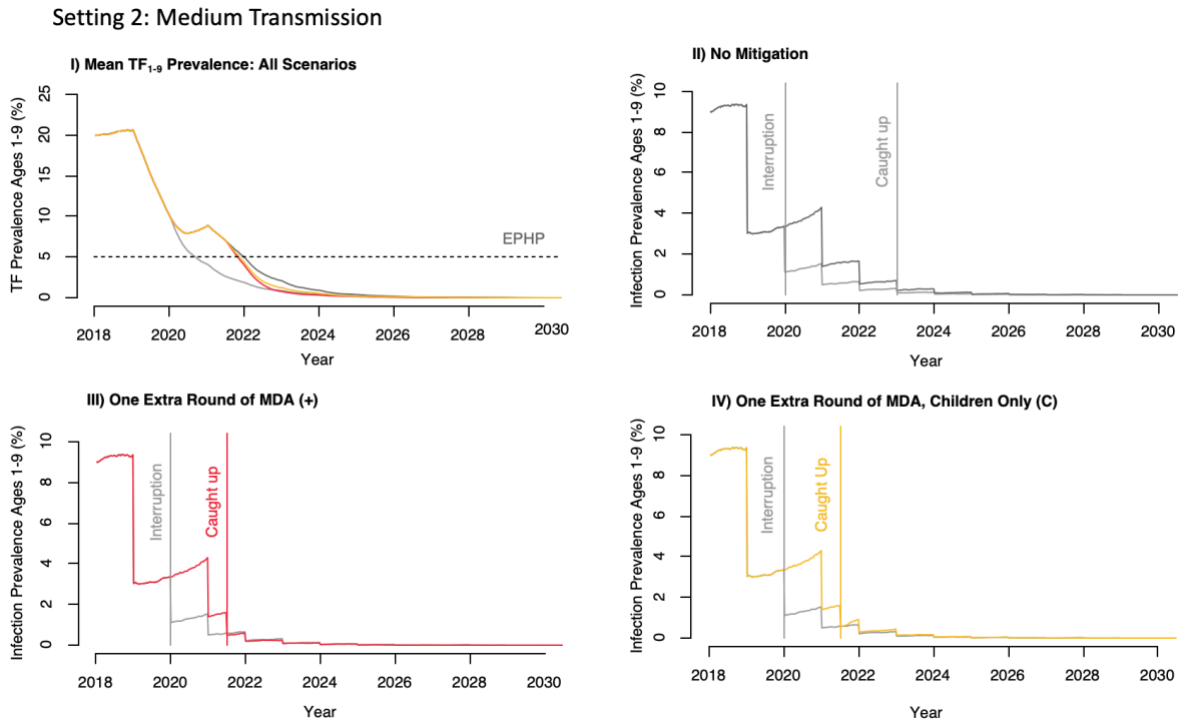


Figure 15: Medium transmission (Setting 2). Mean prevalence of TF in children aged 1-9 and progress towards EPHP threshold under different modelled scenarios (Panel I); Mean prevalence of trachoma infection in children aged 1-9 (Panel II-IV). The light grey curve represents no disruption, disruption to treatment scenarios with no mitigation is plotted as dark grey, and mitigation strategies targeting the whole community (+) and children only (C) are plotted as red and yellow respectively.

Table 7: Summary of model output for Settings 1 and 2 (Confidence Intervals are given as 95th and 80th Centiles).

Setting 1: High Transmission	**Mean years to achieve EPHP (Median; 80% CI)**	**% reaching TF_{1-9}<5% after 6 rounds of MDA**	**Mean % TF in children after 6 rounds MDA (95% CI);**
No interruption	4.37 (4.15; 2.92, 7.29)	88.1	1.70 (0, 12.85)
No mitigation	7.06 (6.25; 2.92, >15)	69.9	4.07 (0, 19.86)
Extra round: (+)	5.31 (5.23; 2.92, 9.58)	81.6	2.1 (0, 12.81)
Extra round: Children (C)	5.40 (5.33; 2.92, 9.57)	77.9	2.84 (0, 15.21)
Setting 2: Medium Transmission	**Mean years to achieve EPHP (Median; 95% CI)**	**% reaching TF_{1-9}<5% after 4 rounds of MDA**	**Mean % TF in children after 4 rounds MDA (95% CI);**
No interruption	2.69 (2.62; 1.83, 4.64)	98.7	0.88 (0, 4.17)
No mitigation	4.0 (3.85; 1.83, 5.73)	97.1	0.93 (1.58, 5.20)
Extra round: (+)	3.83 (3.75; 1.83, 4.58)	99.2	0.45 (0, 3.19)
Extra round: Children (C)	3.89 (3.81; 1.83, 4.90)	99.0	0.76 (0, 4.08)

Summary

- In high transmission settings, missing a single round of treatment will on average lead to an increase in the number of MDA rounds needed to reach elimination targets. On average, without mitigation, it will take 2.7 years to catch-up.
- In high transmission settings, an additional round of MDA in the year after programmes are resumed will accelerate catch-up, and progress towards elimination targets will only be delayed by approximately 1 year.
- In medium baseline prevalence settings (which are on track for EPHP after 3-4 rounds of MDA), the impact of missed MDA will be less profound. In most cases, EPHP targets will still be reached after the same number of treatment rounds.
- It is noteworthy that there are a finite number of districts (estimated less than 60 worldwide) where models suggest that under a strategy of annual MDA control will not be achieved before 2030 (the reproductive number under treatment, or R_T, is greater than 1), and alternative strategies may need to be considered if control is to be achieved. Here the impact of interruptions due to COVID-10, including in terms of excess morbidity, will be even greater, and the need for mitigation and a change in control strategy post-2020 is amplified.
- Further work using the GET2020 database aims to identify which districts currently mid-way through trachoma control programmes will most benefit from post-interruption mitigation strategies.

Further details

For both settings, 2000 simulations of a population of size 1000 are considered, with no effect of migration. To account for the individual-level nature of the model, Poisson distributions are used to assign infection/disease periods for each individual, with parameters regarding maximum/minimum duration of infection/disease used by Pinsent and colleagues (2018) given as average values. The decay rate for subsequent infections is as given in Pinsent and colleagues (2018). The transmission rate (given as Beta in Pinsent *et al*., 2018) is varied in order to simulate the range of baseline prevalences in the two settings, and these are filtered to allow the baseline TF prevalence in children aged 1-9 in the high transmission setting to vary between 37.5 and 42.5 (mean 40) and in the medium transmission setting to vary between 17.5 and 22.5 (mean 20). In estimating the probability of reaching the EPHP threshold after 4 rounds of community-level MDA (medium prevalence setting) or after 6 (high prevalence), it is assumed an impact survey is carried out at 12 months after the previous MDA. Treatment is assumed to be distributed randomly. The potential additional reduction in transmission afforded by WASH and facial cleanliness and environmental improvement (F&E) interventions is not currently incorporated due to uncertainty about the impact of these strategies. In the scenarios with extra MDA rounds in the year following the disruption, these are simulated to occur 6 months after the first round. However, previous work by members of the Consortium indicates that if the timing of catch-up rounds varies due to operational constraints, the anticipated impact of mitigation strategies would be equivalent (Gao *et al*., 2016).

Generalization of results

To address the geographic variability of trachoma transmission and the unknown time that COVID-19 will disrupt MDA, we developed a simplified susceptible-infected model of trachoma transmission. This simplified model consists of periods of the exponential growth of infection that are punctuated by regularly spaced reductions in infection due to MDA. We define the 'programmes delay' as the time that a MDA cycle is delayed due to circumstances such as the COVID-19 pandemic. We define the 'elimination delay' as the time gap between MDA disruption and a return to the level of infection prior to the disruption (**Figure 16**).

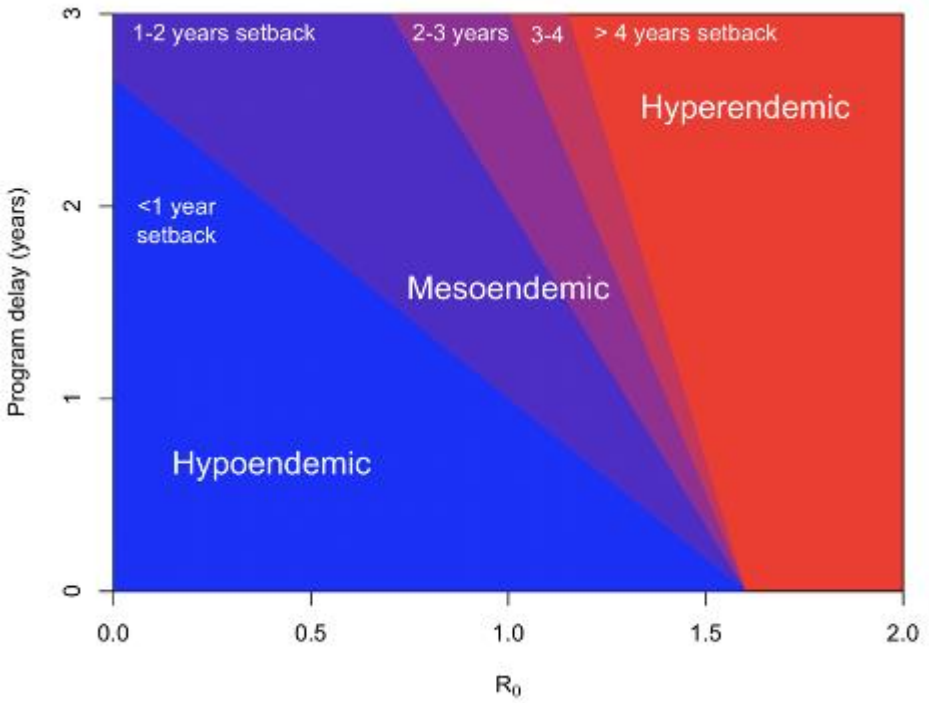


Figure 16: The elimination delay for achieving trachoma control in a given community is coloured according to the R_0 and the programmes delay for the administration of MDA. The underlying model assumes annual MDA, and assumes MDA leads to an instantaneous 70% decrease of trachoma incidence. Hypoendemic ($R_0 < 1$), refers to regions in which transmission is expected to be self-limiting, mesoendemic ($1 < R_0 < 1.6$) refers to conditions in which annual MDA will be sufficient to reach control targets and hyperendemic refers to regions ($R_0 > 1.6$) which require a new paradigm of treatment for eventual control. The half-life for infections is assumed to be 0.5 years.

Visceral leishmaniasis on the Indian sub-continent

Visceral leishmaniasis (VL), also known as kala-azar, is caused by *Leishmania* parasites and transmitted by sand flies. WHO initially targeted VL for elimination as a public health problem (EPHP) on the Indian subcontinent (ISC) by 2020, defined as <1 VL case per 10,000 population at the district level in Nepal and sub-district level in Bangladesh and India. For validation of the EPHP target, the incidence needs to be below the target for a minimum of three consecutive years (World Health Organization Regional Office for South-East Asia, 2016). More recently, WHO has also targeted for validation of EPHP in 85% of countries by 2030, defined as <1% case fatality rate due to primary VL disease. The main interventions to achieve both the 2020 and the new 2030 targets are vector control through indoor residual spraying of insecticide (IRS) and reducing the duration between the onset of symptoms and start of treatment by active case detection (ACD).
Inevitably, the spread of Covid-19 on the ISC in 2020 will impact the implementation of the VL control programme and thus the progress towards achieving the targets. On the 25th of March 2020, India declared a nationwide lockdown and it is likely that both IRS and ACD efforts will be suspended temporarily.
With this study we:

1) predict if the interruption of the VL control programme will erode previous gains, and
2) explore the potential benefits of implementing mitigation strategies once the programme resume.

Modelling approach, scenarios and mitigation strategies

To study the impact of COVID-19 on the VL transmission dynamics, we have used an established deterministic transmission model developed at Erasmus MC, also known as 'model E1', for which detailed descriptions are given by Le Rutte *et al*. (2016, 2017, 2018, 2019). With this model, we simulate the transmission of VL between humans and sandflies on the Indian subcontinent. The model is age-structured, and all parameter values are based on previous estimates (Le Rutte *et al.*, 2016, 2017). Highly endemic settings are considered to have a pre-control endemicity of ~10 VL cases per 10,000 population per year and moderately endemic settings of ~5/10,000/year. The model incorporates IRS coverage through a reduction in the sand fly biting rate, and ACD through a decrease in the average detection delay of symptomatic cases.

According to the WHO guidelines, VL control starts with five years of '**attack phase'** which is followed by the '**consolidation phase'.** These phases entail different levels of IRS and ACD, as described in the legend of **Figure 17**. We assume that VL control would have been implemented as recommended by WHO, when uninterrupted by COVID-19.

In addition to the 'no interruption' scenario, we consider an alternative scenario that could result from the impact of the current COVID-19 pandemic. For this scenario, we consider an interruption of the VL control programmes of one year (1 April 2020 - 1 April 2021) starting about 2 years after the start of the attack phase. We simulate that during this time no IRS

takes place and that the duration until treatment is increased to the pre-control level without ACD. We assume passive case detection followed by treatment is still in place and that the detection of PKDL remains unchanged in these simulations.

To reduce the potential health burden caused by missing one year of IRS and ACD we also present the potential impact of implementing a mitigation strategy, simulated as a one-year extension of the attack phase.

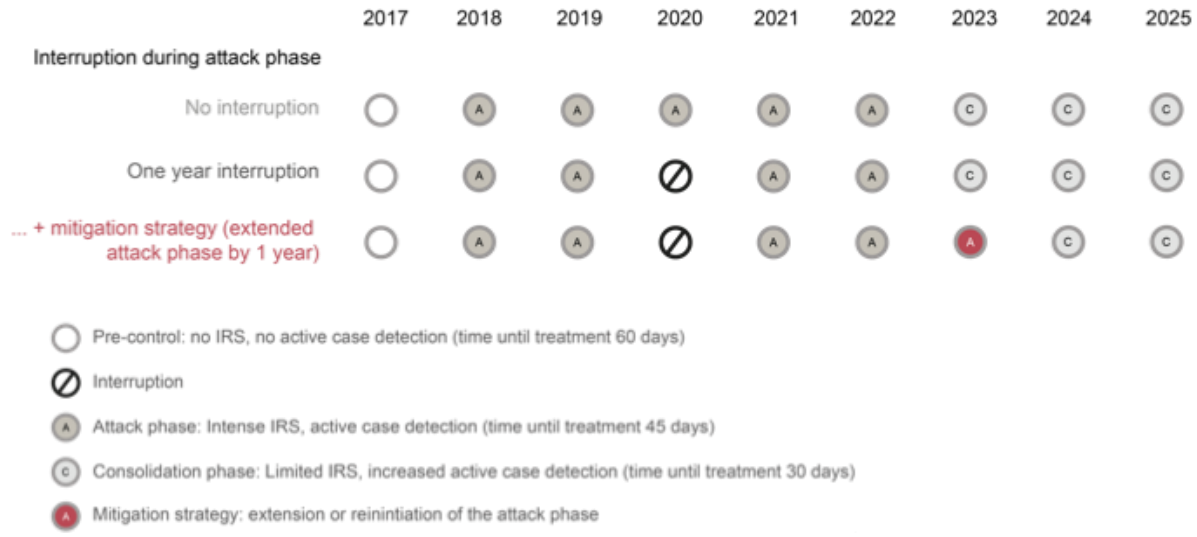


Figure 17: Visual representation of the scenarios and mitigation strategies modelled for VL. Both a setting with a highly and moderately pre-control endemicity are simulated. IRS = indoor residual spraying of insecticide, ACD = active case detection. The interruption due to Covid-19 runs from 1 April 2020 - 1 April 2021.

Model outputs

With regard to the first question whether the impact of COVID-19 could erode all previous gains, the model predicts that not all previous gains from the programme will be lost. However, we can expect an increase in VL incidence with long-lasting effects.

Figure 18 presents the default scenario in light grey. The dark grey line visualises the predicted VL incidence over time for a one-year of programmes interruption. In highly endemic settings, achieving the target incidence could take 9 years in the 'no interruption' scenario. A one-year interruption during the attack phase of the control programme is estimated to cause a delay to reach the EPHP target of ~1.5 years. In moderately endemic settings the target incidence is normally estimated to be achieved within 2.5 years of starting the programme. There, a one-year

interruption to the programme is expected to cause a delay of nearly 2 years. **Table 8** provides an overview of these delays until reaching EPHP per setting, measured as the first moment the VL incidence hits the 1/10,000/year target line which is continued for a minimum of three years.

For our second question, we explored the benefits of implementing a mitigation strategy once the programme resumes. To mitigate the delays to the target, an extended duration of the attack phase, here similar in length to the duration of the interruption, can reduce the delays to the target with about one year in previously highly endemic settings. In moderately endemic settings, such a mitigation strategy proves no additional impact as the target is estimated to be achieved before the start of the mitigation strategy. In settings that have already achieved the target previously to the Covid-19 pandemic, VL incidences can increase to above the target again. The impact of the mitigation strategy is presented with red lines in **Figure 18** and is summarized in **Table 8.**

When interpreting the results, it is important to note that the results are dependent on the pre-control VL incidence level and timing of the interruption during the control programmes. In different settings a one-year interruption could lead to as much as a 6-year delay to the target. We have simulated a population at the scale of a Indian sub-district level. At a smaller geographical scale, such as village level, the effect of an interruption of control measures should be expected to be more variable, ranging from nothing to outbreaks as observed in Kosra (Kumar, 2020). The latter was most likely influenced by the migration of people in and out of the area, a phenomenon that was also observed at the start of the Indian lockdown at the end of March 2020.

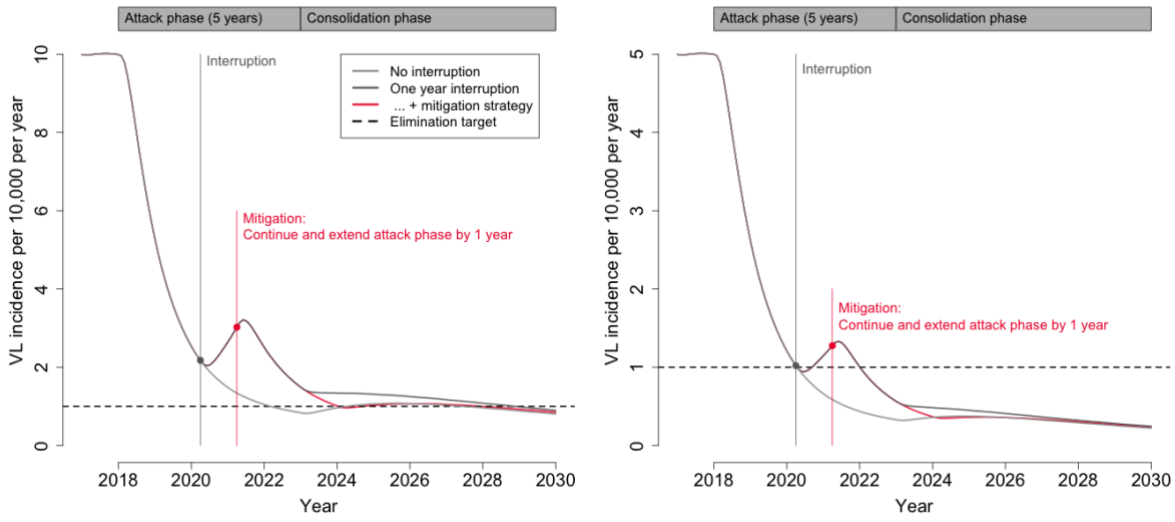


Figure 18. Predicted visceral leishmaniasis incidence over time. The grey bars at the top represent the 'no interruption' scenario as presented in Figure 17. Interruptions to the programmes are simulated from 1 April 2020 to 1 April 2021. The left panel represents a former highly endemic setting (10/10,000/year), the right panel presents a former moderately endemic setting (5/10,000/year).

Table 8. Delays until reaching EHPH for all settings and scenarios

	Time to EPHP	Delay to EPHP	
Timing of interruption *Setting*	**No interruption**	**1 year of interruption**	**1 year of interruption + mitigation** *(reduction)*
Attack phase *High*	9.5 years	~1.5 years	0.5 years *(~1 year)*
Attack phase *Moderate*	2.5 years	~2 years	~2 years *(none)*

Summary

- In the simulated settings, a one-year interruption of the VL control programmes causes 1.5-2 years delay to achieving EPHP.
- Extending the attack phase by one year could reduce the delay to EPHP in highly endemic settings.
- In settings that have already achieved the target previously to the COVID-19 pandemic, VL incidences can increase to above the target again.

Further details

The model is calibrated based on age-structured data from approximately 21,000 individuals included in the KalaNet bednet trial in India and Nepal (Picado *et al.*, 2010). The impact of IRS was estimated using geographical cross-validation on >5,000 VL cases from 8 endemic districts in Bihar collected by CARE India (Jervis *et al.*, 2017) for which the full model descriptions and sensitivity analyses are presented in Le Rutte, Chapman *et al*. (2017). The exact impact of ACD and IRS on VL incidence remains debated, and therefore requires further investigation.
With the uncertainty of the exact impact of Covid-19 on the control programmes, we decided to apply the pessimistic assumption of the complete withdrawal of all ACD and IRS activities. However, would for example only one round of IRS take place (instead of the default two), the impact would be smaller than what we predict here.

Besides our simulations of VL on the Indian subcontinent, the global WHO VL 2030 target (85% of countries reaching <1% case fatality rate due to primary disease) is also likely to be impacted by the global interruption of the programme due to Covid-19.

The results of this preliminary study are to be interpreted as a first insight into the potential impact of the Covid-19 pandemic on VL incidence on the Indian subcontinent. For a more detailed understanding of this impact and the potential mitigation strategies, subsequent analyses are being performed. These simulations also consider settings that are currently in the consolidation phase and take into account different durations of interruptions as well as various alternative mitigation strategies.

Gambiense Human African Trypanosomiasis (gHAT)

Gambiense human African trypanosomiasis (gHAT) is a vector-borne disease targeted for elimination of transmission (EOT) by 2030. Strategies against gHAT consist primarily of medical interventions - either active screening (AS) or passive surveillance (PS) - which are used to diagnose and treat infected people. Whilst vector control (VC) is implemented in some settings, its use is not widespread. AS of endemic villages typically happens once per year, whilst PS allows symptomatic individuals to self-present at fixed health facilities. gHAT is a disease with slow progression, where people generally remain infected over several years in the absence of AS. It also has a low transmission potential even with minimal control effort (estimates of R_0 are around 1-1.3 (Rock *et al.,* 2017; Funk *et al.,* 2013)).

The 2014/15 West African Ebola outbreak serves as a recent example of disruption to gHAT control activities: during this period all medical gHAT activities were either suspended (AS) or scaled back (PS) in Guinea with only existing VC continuing at pre-Ebola levels. Following the reinstatement of medical activities after the end of the epidemic, there was a large increase in case detection, except for the region with VC where there were no detected cases (Kagabadouno et al., 2018). It is estimated that there could have been up to a 10-fold increase in disability-adjusted life years (DALYs) lost due to this Ebola-related scale back (Camara *et al.,* 2017).

Modelling approach, scenarios and mitigation strategies

In the present study, we focused on four potential interruption scenarios of gHAT activities due to COVID-19. We consider settings in which VC has not yet been implemented and explore the impact of either interruption to screening activities in either only 2020 or in both 2020 and 2021. In all scenarios, we consider AS is suspended, in combination with, either continuing PS or the additional suspension of PS for the same time duration. We focus here on “high-risk” and “moderate-risk” settings with average levels of AS before and after the interruption.

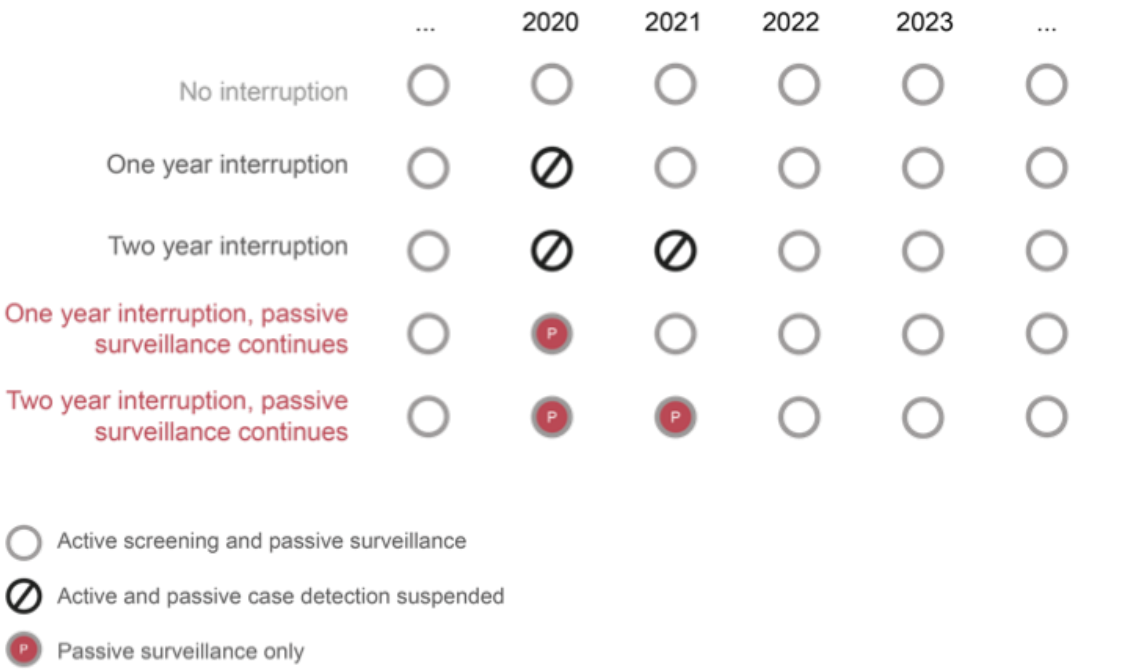


Figure 19: Visual representation of the scenarios and mitigations strategies modelled for gHAT. For all scenarios, simulations are performed for both high- and moderate-risk settings.

Two previously published deterministic models (Model S and Model W) were used to perform this analysis. Both were originally calibrated to human case data in the Democratic Republic of the Congo (DRC) (Castaño *et al.,* 2020; Crump *et al.,* 2020), which has around 69% of the case burden in 2018 (WHO, 2019). Both models explicitly include a tsetse vector component and have a high/low-risk structure for human exposure to tsetse and participation in AS. Neither model includes animal reservoirs or importation. Models S and W were calibrated to a high-risk and moderate risk setting respectively. Model S simulated 10% annual AS, and Model W simulated 16% AS. PS rates for non-interruption years were inferred through the fitting. AS was assumed to take place at the beginning of each non-interruption year, whereas PS occurs throughout the year.

Model outputs

Key outputs of our models are annual new infections (see **Figure 20**), disease-induced deaths and the expected year of EOT (see **Table 9**). Decreasing trends in annual incidence are expected to continue in both moderate- and high-risk settings, albeit at lower rates, even with the full or partial interruption of screening, except for the scenario where all screening is interrupted for two years, where there is an increase in the second year of interruption.

Whilst not shown here, we expect high variability in case reporting during and after the COVID-19 interruption. In years of interruption, cases are anticipated to decline substantially, followed by a high level of case reporting after the resumption of activities. The increase of detected cases after interruption does not necessarily indicate that transmission has increased and could occur even if the transmission has plateaued or has slightly decreased during interruption due to the delay of diagnosis of infections acquired during the interruption.

gHAT is a disease with slow progression and as such, the impact of interruption of control activities for one or two years may be minor in moderate-risk settings, with EOT delayed by similar timescale as the interruption. High-transmission settings may not reach the 2030 target regardless of interruption, and in those settings, interruption would translate into higher levels of disease-induced mortality in the coming years.

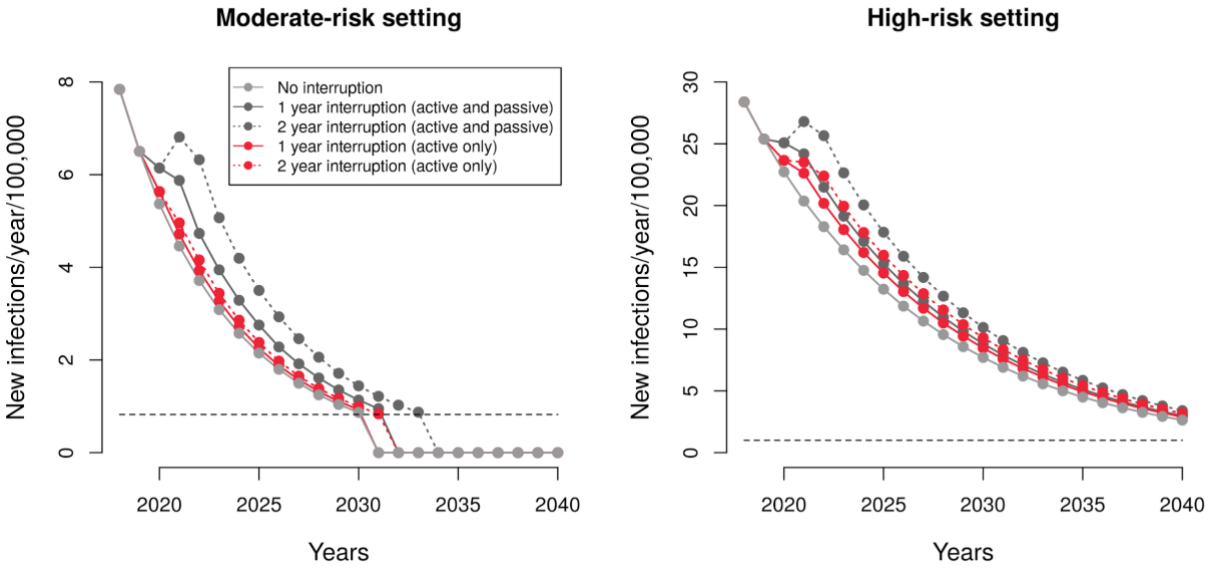


Figure 20. Projections on the annual new infection (transmission to humans) incidence under different scenarios for a moderate- (left) and high-risk setting (right). Note that the scales on the y-axis are different on the two plots.

Table 9: Delay to achieving EOT goal, years (median and 95%CI) as the impact of interrupting screening activities in high- and moderate-risk settings, plus expected time to goal (from 2018) if no interruption. Timeframes >12 years would not reach EOT by 2030

Risk setting	**Moderate**	**High**
Time to the goal if no interruption	13 (5-29)	30 (24-41)
Delay to goal in scenario 1 (no AS or PS, 1-year interruption)	1 year (1, 2)	1 year (1, 2)
Delay to goal in scenario 2 (no AS or PS, 2 years interruption)	3 years (2, 4)	3 years (2, 4)
Delay to goal in scenario 3 (no AS, 1-year interruption)	0 years (0, 1)	1 year (1, 2)
Delay to goal in scenario 4 (no AS, 2 years interruption)	1 year (0, 2)	2 years (1, 3)

Summary

- Delays incurred with interruption of active screening (AS) only (red lines) will be small in both moderate- and high-risk settings.
- There could be recrudescence of infection in the second year of interruption if both AS and passive surveillance (PS) are stopped (dark grey dashed).
- High-risk settings may have already required intensified interventions to meet EOT by 2030.
- Retaining PS can help prevent substantial (temporary) increases in mortality.

Further details

Model S was fitted to former Bandundu provincial level 2000-2012 screening and case data (Castaño *et al.,* 2020) whilst Model W was fitted to similar data at the health zone level for Mosango health zone, DRC (Crump *et al.*, 2020). Whilst both models take mean AS from the last five years of data, underlying data in each model calibration leads to different levels of the population screened in projections: 16% in the moderate risk setting and 10% in the high-risk setting. The outputs presented here are designed to be illustrative; future work will be needed to explore the impact of COVID-19 interruptions on specific locations based on their highly heterogeneous prevalences and AS coverages. Such work could also simulate other more nuanced strategies including increasing AS or introducing VC following the interruption, which are both expected to reduce time to EOT and therefore mitigate against negative impacts of COVID-19.

The interruption scenarios considered here are very general as it is unclear exactly how long the current COVID-19 outbreak will last and what services will be impacted. By taking the extremes of no PS or continuation of previous PS we believe that any partial PS remaining in place will fall between these results.

The mathematical framework used for deterministic models means that transmission can asymptotically approach but never reach zero; and as such we have used a proxy threshold for EOT of <1 new infection per health zone population size (~100,000) to compute when EOT has been achieved (Rock *et al.,* 2018; Castaño *et al.,* 2020). At extremely low prevalence, a stochastic model formulation is more suitable to forecast EOT timelines (Castaño *et al.,* 2019) and such model frameworks will be used in future analyses.

We do not consider the animal transmission of gHAT here, although there is limited evidence suggesting it may be a potential threat to EOT. We do not explicitly incorporate asymptomatic human infection, although the models implicitly allow for long time scale infectious durations (through an exponential distribution) - but without spontaneous self-cure.

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