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The potential public health impact of COVID-19 on malaria in Africa

Ellie Sherrard-Smith[#1], **Alexandra B. Hogan**[#1], **Arran Hamlet**[#1], **Oliver J. Watson**[#1], **Charlie Whittaker**[#1], **Peter Winskill**[1], **Fatima Ali**[2], **Audu B. Mohammad**[2], **Perpetua Uhomoibhi**[2], **Ibrahim Maikore**[2], **Nnenna Ogbulafor**[2], **Jamilu Nikau**[2], **Mara D. Kont**[1], **Joseph D. Challenger**[1], **Robert Verity**[1], **Ben Lambert**[1], **Matthew Cairns**[3], **Bhargavi Rao**[4], **Marc Baguelin**[1], **Lilith K. Whittles**[1], **John A. Lees**[1], **Sangeeta Bhatia**[1], **Edward S. Knock**[1], **Lucy Okell**[1], **Hannah C. Slater**[1,5], **Azra C. Ghani**[1], **Patrick G.T. Walker**[1], **Okefu Oyale Okoko**[2], **Thomas S. Churcher**[1,†]

[1]MRC Centre for Global Infectious Disease Analysis Imperial College London, London, UK

[2]National Malaria Elimination Programme, Abuja, Nigeria

[3]Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, London, UK

[4]Manson Unit, Médecins Sans Frontières (Operational Centre Amsterdam), London, UK

[5]PATH, Seattle, USA

[#] These authors contributed equally to this work.

Abstract

Malaria burden is heavily concentrated in sub-Saharan Africa (SSA) where cases and deaths associated with COVID-19 are rising. In response, countries are implementing societal measures aimed at curtailing transmission. Despite this, the COVID-19 epidemic could still result in millions of deaths as local health facilities become overwhelmed. Advances in malaria control this century have been largely due to distribution of long-lasting insecticidal nets (LLINs), with many SSA countries planning campaigns for 2020. Here we use COVID-19 and malaria transmission models to estimate the impact of disruption of malaria prevention activities and other core health services under different COVID-19 epidemic scenarios. If activities are halted, the malaria burden in 2020 could be more than double that of 2019. Mitigating this negative impact is possible, and LLIN distributions in particular should be prioritised alongside access to antimalarial treatment to prevent substantial malaria epidemics.

As witnessed globally, COVID-19 has the potential to overburden health systems. Restrictions to movement, absenteeism, behavioural change, closure of institutions and interruption of supply chains are expected to result in malaria prevention activities being scaled back. These activities include mass distribution of long-lasting insecticide treated nets (LLINs), which are the most effective current tool for reducing malaria[1]. LLINs are

[†]Corresponding author.

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typically distributed centrally within a community at gatherings that may be cancelled or poorly attended as COVID-19 spreads. Other important focal preventative measures such as seasonal malaria chemoprevention (SMC) and indoor residual spraying of insecticide (IRS), which are conducted house-to-house, could also be reduced. The World Health Organization (WHO) has stressed that all routine prevention and case management should be continued to the extent possible[2], but early statistical modelling suggests that disrupting LLIN distribution and treatment could have substantial impact on malaria burden[3].

Here, we attempt to quantify the impact of the spread of COVID-19 on *Plasmodium falciparum* malaria morbidity and mortality in Nigeria and across sub-Saharan Africa using mathematical models of COVID-19[4] and malaria[5]. We assume that one disease does not directly influence the transmission or severity of the other, but that COVID-19 impacts malaria via the response to the epidemic and its repercussions on health systems. Predictions of the timing of COVID-19 epidemics across African countries are highly uncertain and will vary according to how countries respond to COVID-19. We use illustrative examples to show how different COVID-19 mitigation and suppression strategies could influence malaria burden. The pervasive and potentially large consequences of COVID-19 on society, such as increased poverty, malnutrition and social instability, which themselves may influence malaria burden, are not captured.

We consider four scenarios for the COVID-19 epidemic which will determine the period of malaria service interruption (Figure 1):

1) Unmitigated COVID-19 epidemic − whilst unlikely to occur this scenario illustrates how a rapid epidemic would be highly disruptive to malaria services but for a limited period.

2) Mitigation − social contact is reduced but the effective reproduction number (Rt) remains above 1 causing a longer-lasting COVID-19 epidemic.

3) Suppression − social distancing reducing $R_t<1$ remains in place until alternative strategies to contain COVID-19 are available with malaria activities potentially disrupted for a year.

4) Suppression lift − suppression is sustained but then subsequently lifted resulting in a “second wave” COVID-19 epidemic.

We assume that malaria services could be interrupted if COVID-19 mitigation or suppression activities are ongoing or if health care capacity is exceeded due to COVID-19. The impact of different levels of malaria service interruption are investigated. LLIN campaigns can either continue as normal or be delayed for a year, whilst clinical case treatment and SMC either remain as planned, are reduced, or halted.

It is unclear how COVID-19 will spread in Africa although all four COVID-19 scenarios are projected to result in substantial additional deaths from malaria. Implementing COVID-19 mitigation strategies substantially reduces COVID-19 mortality but the prolonged period of health system disruption risks considerably increased malaria deaths (Table 1). This is especially evident in Nigeria where the long malaria service disruption due to COVID-19 epidemic overlaps with the malaria transmission season (Figure 1). Considering impact

over the coming year for the COVID-19 mitigation scenario across SSA, if SMC and IRS were halted, the treatment of clinical cases was reduced by half for the next 6 months, and LLIN campaigns due in 2020 were cancelled, malaria cases are estimated to increase by 206 million (95% Uncertainty Interval, UI, 157−254 million) (Supplementary Table 1), and malaria deaths by 379,300 (95% UI 221,400−537,300) (Table 1), with a corresponding additional 19 (95% UI 11 −26) million life-years lost (Supplementary Table 2).

Many countries are pursuing strategies to suppress COVID-19 to minimise deaths[6]. Our results illustrate that even if COVID-19 suppression is well-managed and LLIN campaigns remain unaffected, with SMC coverage and case management reduced by 50% relative to the norm, the prolonged service interruption could increase malaria deaths in Nigeria by approximately 42,300 (95% UI 22,200−62,300)(Supplementary Table 3) and across SSA by 200,000 (95% UI 114,700−285,200) (Table 1). The impact of this longer disruption to malaria services will be greatest in countries where the malaria transmission is high at the end of the year (Supplementary Figure 1). Failure to maintain a COVID-19 suppression strategy is likely to lead to a large second wave potentially resulting in worse outcomes for both COVID-19 and malaria.

We find that provision of LLINs is critical. Twenty-seven out of 47 malaria-endemic countries in SSA were due LLIN campaigns in 2020 with delivery of 228 million LLINs expected (https://netmappingproject.allianceformalariaprevention.com/). Across SSA, maintaining routine LLIN distribution in a COVID-19 mitigation scenario is predicted to halve deaths (Table 1). Many LLINs in SSA will be three years old and have diminished efficacy due to insecticide loss and physical degradation. The increased spread of mosquitoes resistant to LLIN insecticides may exacerbate this problem[7]. Impact can vary substantially within countries according to existing LLIN protection and whether COVID-19 will delay scheduled LLIN campaigns (Figure 2A, Supplementary Figure 2).

Disruption to case management increases the case fatality ratio (Supplementary Table 4) and is predicted to have similar impact on morbidity to cancelling LLIN campaigns if services are stopped for equivalent time periods (illustrated in the COVID-19 suppression scenario when both LLIN and clinical treatment are interrupted for a year, Table 1). Some level of case management will hopefully remain. Maintaining 50% of the normal level of treatment over a 6-month period may still prevent up to 100,000 deaths if prevention activities ceased. In Nigeria, case management was estimated to be particularly important due to mass LLINs campaigns scheduled in just 7 of the 37 states through 2020. SMC is currently implemented in the Sahel region of West Africa, reducing its continental impact. However, the consequences of cancelling SMC in operational regions is predicted to be large, with SMC reducing deaths by 40% in a COVID-19 mitigation scenario if LLIN distributions and case management are also halted (Supplementary Table 5).

There is considerable uncertainty in how COVID-19 will spread in Africa and how countries will respond[8,9]. A lower basic reproduction number, R0, would slow the epidemic and reduce COVID-19 deaths, yet potentially increase malaria mortality due to prolonged anti-malarial service interruption. It is unclear how effective social-distancing measures to reduce the spread of COVID-19 will be, how long they will be maintained for and their impact

on healthcare capacity (Supplementary Figure 3). This uncertainty substantially influences COVID-19 mortality but also the interruption of malaria services. For example, in Nigeria, if COVID-19 spreads with an R0 of 2.5 compared to 3, service interruption in the COVID-19 mitigation scenario would be extended from 6 to 9 months to prevent a second peak of COVID-19 (Supplementary Figure 3), increasing additional malaria deaths by ~17% even if LLINs were distributed and some case management was maintained (Supplementary Table 6). Overall, the impact of COVID-19 on malaria is predicted to be greater than early estimates by the WHO[3]. This is likely due to the inclusion of SMC and IRS in our analysis, which have substantial public health impact. The model also mechanistically captures differences in population immunity (determined by the history of malaria infection) and the impact of insecticide-resistant mosquitoes, both of which can increase malaria resurgence. Nevertheless, the numbers of deaths presented here should be considered illustrative as there are large uncertainties in how COVID-19 will spread and communities respond.

Following the 2014 West African Ebola crisis, the WHO now recommends the use of mass drug administration (MDA) to prevent excess mortality during complex emergencies[10]. We explored the extent to which introducing or extending chemoprevention could mitigate any excess malaria deaths. If LLIN campaigns in 2020 are delayed during a mitigated COVID-19 scenario, increasing the target age of SMC across the Sahel region from children under 5 years to children under 10 and 15 years could save 13,500 and 22,400 lives respectively (Figure 2B, Supplementary Figure 4A, Supplementary Table 7). Almost half of these lives saved are in Nigeria SMC regions (Supplementary Table 8). Outside current SMC areas, a single round of MDA to 70% of the population is predicted to avert up to 266 deaths per million people over the next year (Supplementary Figure 4B, Supplementary Table 9) depending on where it was implemented (Supplementary Figure 4B, 5 and Supplementary Table 10). Such emergency measures will depend on the feasibility of increasing the supply of appropriate drugs in areas where such interventions are not currently planned.

Symptoms of both COVID-19 and malaria include fever, which may confuse diagnosis in settings with limited testing for both diseases. In COVID-19 cases the likelihood of developing fever increases with age (Figure 3A), whilst malaria fever declines. The percentage of fevers due to malaria compared with COVID-19 is predicted to vary temporally according to the synchrony of the two epidemics (Figure 3B-C). Many countries are advising that suspected COVID-19 cases should self-isolate (www.acaps.org/covid19-government-measures-dataset) which may further reduce malaria diagnosis. Providing simple age-based guidelines could substantially reduce malaria burden if malaria tests are unavailable. For example, presumptively treating 70% of febrile children under 5, 10 and 15 years with antimalarials could save 122,000, 159,000 and 178,000 lives over the next year respectively. Further work is needed to consider the implications of this on the supply of drugs and burden of non-malarial fevers[11]. Adhering to social-distancing guidelines will also remain critical as many people who are infected with COVID-19 could also harbour malaria parasites. For example, our modelled results indicate that at the malaria transmission season peak in Mali (an example of a country with seasonal transmission, Figure 3B), in individuals older than 15 years, 30% of those infected with COVID-19 would also have malaria parasites, and therefore may not self-isolate if diagnosed with malaria as the cause of their fever.

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The rapid global spread of the SARS-CoV-2 virus has demonstrated our global vulnerability to new infectious diseases. Continued malaria prevention and treatment will be essential to reduce pressure on health systems in the year ahead.

Online methods

COVID-19 transmission model

Potential COVID-19 trajectories were produced through a modelling framework from Walker et al[4]. We used an age-structured SEIR model of transmission with age-specific patterns of disease severity captured according to age-dependent probabilities that infection leads to disease requiring hospitalisation (and the need for treatment with high-pressure oxygen), to more severe disease requiring intensive care and subsequently to mortality. Model parameters are based on analysis of age-specific severity and infection-mortality ratios observed in China and the UK[4,12,13] since comparable data from sub-Saharan Africa are currently not available. To produce simulations representative of a malaria endemic setting, the model was calibrated to typical social contact patterns observed within surveys in sub-Saharan Africa (SSA), which show less substantial declines in contact rates by age[14], and the demography of Nigeria, our case study and the country with the highest burden of malaria globally[15]. Our projections therefore incorporate a lower per-infection demand for healthcare such as oxygen and mechanical ventilation driven by the younger populations within malaria endemic settings. Life-years lost were calculated under this demography using the corresponding life tables.

To capture the likely constraints within a health system, we contrasted this demand for healthcare with a representative level of supply using the median estimated provision of hospital beds and intensive care units for a low-income country[4]. This threshold was chosen on the basis that, although many countries in SSA are lower-middle-income and therefore likely to have a lower total number of hospital beds and intensive care units, access to high pressure oxygen and mechanical ventilation within hospitals is lower than within equivalent high income settings[16]. During the course of a projected scenario, as healthcare capacity is exceeded, individuals requiring either mechanical ventilation or high pressure oxygen who are unable to receive these interventions are then subject to a substantially higher degree of mortality, leading to excess mortality during time-periods in which health systems are overwhelmed (for full details, code and parameterisation see https://github.com/mrc-ide/squire (accessed June 09, 2020)).

Representative scenarios were simulated using a basic reproduction number, R0, of 3 representing a 3.5 day doubling time in cases and deaths reflective of many trajectories currently observed globally[17]. A full list of the parameter values is provided in Supplementary Table 11. Once a threshold of 0.1 deaths per million (approximately reflecting the COVID-19 mortality observed in many countries in Africa to date) is exceeded, the pandemic trajectory follows four potential scenarios:

- *"Unmitigated":* no direct action is taken but contact rates are reduced by 20% relative to baseline according to assumed behaviour change given the pandemic even in the absence of specific, coordinated public health interventions.

- *"Mitigation":* through combinations of isolation and social distancing, contact rates are reduced by 45% for 6 months after which infections fall to low levels and contact rates return to pre-pandemic levels. This scenario approximates the maximum reduction in the final size of the epidemic that can be achieved whilst generating sufficient levels of immunity capable of preventing a second wave once measures are lifted (assuming infection leads to high levels of immunity from reinfection). It thus produces the lowest final numbers of COVID-19 infections of the three strategies that do not involve indefinite suppression.
- *"Indefinite suppression":* stringent suppression-targeting interventions are implemented to reduce contact rates by 75%, and these are maintained indefinitely in the hope that a pharmaceutical intervention (e.g. effective vaccine) is developed and deployed. We run this scenario for 12 months. (After this period, lifting suppression without such a pharmaceutical intervention would lead to a second wave of equivalent size as in the *"Suppression lift scenario".)*
- *"Suppression lift":* the stringent 'lockdown' type interventions implemented by many countries are assumed to reduce contact rates by 75%. This reduction is maintained for two months, then lifted, and contact rates return to 80% of their pre-pandemic levels for the remainder of the epidemic.

These scenarios represent four possible projections of what could happen to the epidemic, not what policy strategy was adopted by the different countries. The number of deaths associated with COVID-19 between 1 May 2020 to 30 April 2021 is estimated for African populations at risk of malaria to provide a direct comparison with the predictions of malaria mortality.

It is assumed that malaria control is impeded by either the health system being overwhelmed or because mitigation or suppression social distancing measures are in place. The health system is classified as being overwhelmed when the model estimates that the number of people currently requiring non-critical care in hospitals for COVID-19 is 50% more than current hospital capacity (here defined for Africa as 1,281 per million people[4]). The timing and duration of service interruption for the different COVID-19 scenarios are shown in the second row of Supplementary Figure 1.

The trajectory of the COVID-19 pandemic in Africa is highly uncertain. To illustrate this uncertainty two different sensitivity analyses are conducted; (i) a univariate sensitivity analysis which shows how R_0 influences the severity of the epidemic, and (ii) a multivariate sensitivity analysis which varies all parameters to indicate the wider uncertainty.

In the univariate sensitivity analysis we vary R0 between 2.0 and 3.5 to cover the range of estimates currently predicted for the region[8,9]. This is repeated for the 4 different COVID-19 scenarios described above. Estimates of the number of people requiring supplementary oxygen over time are presented in Supplementary Figure 3A. Note that in the COVID-19 mitigation scenario when R0 is lower than 3 the epidemic is not predicted to have peaked after 6 months when the social distancing measures are assumed to be lifted (and many people have not been infected). In this scenario, if social distancing measures are relaxed then there is predicted to be a large rebound epidemic with a high death rate as hospitals are

overwhelmed (similar to the suppression lift scenario). This means that lower R0 simulations may counter-intuitively have higher deaths due to COVID-19. An alternative assumption could be that social distancing measures in the mitigation scenario are extended for 9 or 12 months. These simulations indicate a lower peaked epidemic with fewer deaths. Both possible mitigation scenarios with different periods of social distancing are presented in Supplementary Figure 3A.

In the multivariate sensitivity analysis we vary all the main parameters within the model for the 4 different COVID-19 scenarios. These include R0, the effectiveness of social distancing at reducing the contact rate, parameters determining the duration of hospitalisation and the different severity parameters of the disease (the probability of death if critical care is required but not received; probability of death if hospitalised and oxygen is available; probability of death if hospitalised and but oxygen is not available and probability of death if hospitalisation is required by no hospital bed is available). A total of 500 parameter draws were independently sampled using a log-scaled triangular distribution centred around 1 which spanned the range of values presented in Supplementary Table 11. To capture uncertainty in the infection fatality ratio (IFR) and how this varies by age, the probabilities of death reported in Supplementary Table 11 were applied to 500 posteriors sampled from the fitted joint posterior distribution from Verity et al[13]. This provides 500 different estimates of the magnitude of the IFR and how it increases with age. These values were then used to parameterise 500 different simulations of COVID-19 transmission model. For each run the period of potential malaria service interruption were calculated from the introduction of mitigation measures to the time when healthcare is non-longer over capacity (Supplementary Figure 3B-E). Results show how varying the parameters of the COVID-19 mitigation scenario can produce COVID-19 trajectories similar to the other three COVID-19 scenarios considered. For example, high R0 generates short periods of service interruption similar to the unmitigated scenario whilst a low R0 may recreate the period of interruption of either the suppression lift scenario (if social distancing measures are released after 6 months) or a suppression scenario (if social distancing is maintained for a longer period). The uncertainty in the number of deaths from the multivariate sensitivity analysis were used to estimate the mortality 95% uncertainty intervals presented in Table 1.

Malaria transmission model

A previously published model of malaria transmission dynamics was used to predict malaria deaths resulting from different COVID-19 scenarios[5] (code is freely available https://github.com/jamiegriffin/Malaria_simulation). Simulations were run at the administrative 1 unit level (where, for each region, the model is calibrated to capture the seasonality, prevalence, vector composition, treatment coverage and vector control coverage incorporating levels of pyrethroid resistance in each unit) and results are aggregated across regions according to size of the population at risk of malaria. Results are presented for the high malaria burden country of Nigeria and for SSA as a whole. For Nigeria, administrative 1 unit level estimates of malaria prevalence, long-lasting insecticide treated net (LLIN) use, drug treatment, coverage of seasonal malaria chemoprevention (SMC) and the timing of 2020 LLIN campaigns were made available by the National Malaria Elimination Programme (NMEP) in Nigeria (Supplementary Figure 6). For other regions of SSA models were

parameterised using 2016 malaria prevalence from the Malaria Atlas Project (MAP, https://malariaatlas.org/ (accessed September 10, 2018)). For all countries, modelled clinical cases were aligned with World Malaria Report median cases.[15,18] Long-lasting insecticide treated net (LLIN) usage was estimated at the administrative 1 unit level also using MAP estimates, with LLIN usage after campaigns expected to be matched at each subsequent mass campaign. Malaria control depends on insecticide resistance in the local mosquitoes which diminishes the effectiveness of LLINs. This was estimated for each administrative unit from discriminating dose bioassays collated by the World Health Organization over time (projecting forward to 2020) and combined with results from experimental hut trials to estimate the LLINs epidemiological impact[19,20]. Malaria transmission seasonality was estimated by local rainfall trends averaged over eight years and offset by 35 days to reflect mosquito abundance (National Weather Service. Climate Prediction Center. [internet] (cited 24 Mar 2016)[21,22]). The estimated proportion of clinical cases receiving prompt treatment was based on Demographic Health Survey (DHS) data and is assumed to remain at estimated 2016 levels[23]. Malaria deaths across all ages were estimated using the modelled number of severe cases, scaled by the assumed proportion of severe cases resulting in mortality both in and outside the hospital setting, and adjusted by the location-specific proportion of clinical cases receiving treatment[5]. Estimates of malaria deaths in 2018 were scaled to align with World Malaria Report median deaths for 2018 for the same region[15].

Different levels of malaria prevention and treatment interruption are considered together. The impact of the COVID-19 epidemic on malaria is determined solely by the durations of service interruption which vary for malaria prevention and treatment activities according to which of the four different COVID-19 scenarios is considered. The duration of these different periods of interruption of malaria services are presented in Figure 1 and are chosen to be representative of the range of durations observed in the multivariate sensitivity analysis of the COVID-19 model (Supporting Figure 3D). We assume that changing the human-to-human contact rate that influences the trajectory of the COVID-19 epidemic has no impact on malaria transmission other than through the duration of service interruption. The possible impact of COVID-19 on LLIN distribution is assumed to start at the beginning of the COVID-19 epidemic as the majority of African countries initiated some mitigation or suppression activities. The increase in malaria cases caused by COVID-19 will depend on the time since the last LLIN campaign, as older nets are likely less effective due to loss of insecticide[20]. Aging of LLINs may be exacerbated by the spread of insecticide resistant mosquitoes, as they may overcome the concentrations of insecticide on the LLIN earlier than susceptible mosquitoes[7,20]. All LLINs prior to 2020 are assumed to be standard pyrethroid-only LLINs, as the numbers of alternative LLINs procured in 2019 are very low. In Nigeria the year and month of LLIN campaigns is known (or approximated for future mass distributions) at the administrative 1 unit level (state) providing greater resolution. For elsewhere in Africa Alliance for Malaria Prevention (https://netmappingproject.allianceformalariaprevention.com/) estimates were used to calculate the timings of campaigns and the proportion of LLINs distributed in 2018, 2019 and due in 2020 by country as it is unclear when or where the different campaigns were delivered at a sub-national level. Different simulations were run for each administrative unit distributing LLINs at the appropriate year and season. Overall estimates of clinical

cases in the administrative unit were weighted by the proportion of LLINs given out that year. LLIN campaigns due to occur prior to April 2020 were assumed to have occurred as planned. Those campaigns which were due at a time of COVID-19 induced-disruption either went ahead as planned (achieving the same population coverage) or were delayed until a year after they were originally due. LLIN campaigns due in quarters 2−4 in 2020 were assumed to be delayed in the unmitigated, mitigated and suppression lift COVID-19 scenarios. This period of disruption is assumed to be longer than other control interventions, reflecting the high chance of disruption to the LLIN supply chain and difficulties in distributing LLINs to local communities. Standard pyrethroid LLINs were distributed in 2020 unless the region was due to have LLINs with the synergist piperonyl butoxide, and LLIN efficacy estimates were taken from Churcher *et al*[20]. It is assumed that 80% of LLINs are distributed through mass campaigns and the remaining are distributed continually, and that these continual distributions cease if LLIN mass campaigns are delayed.

Uncertainty in the estimated number of clinical cases and deaths and life-years lost was investigated using a multivariate sensitivity analysis. It was not computationally possible to generate full posterior samples for all scenarios presented here. We therefore developed and tested a Normal approximation to the posterior distribution for the output metrics.

First, twenty draws from the joint posterior distribution of the fitted transmission model parameters were used to generate 20 uncertainty runs for all 37 states in Nigeria, for each of the COVID-19 and malaria scenarios (Supplementary Figure 7). For each uncertainty run, we calculated the additional clinical cases and deaths to generate 95% uncertainty intervals for Nigeria, and also calculated the coefficient of variation (CoV). We then tested the applicability of a Normal approximation for uncertainty in other regions by undertaking a full uncertainty analysis across a smaller subset of 40 first administrative units (10 administrative units from each of Zambia (all provinces included), Mozambique, Democratic Republic of the Congo and Burkina Faso) and comparing 95% uncertainty intervals generated for each country to the intervals obtained using a Normal distribution approximation with the CoV for Nigeria. We found good agreement between the approximation and full uncertainty analysis for the regions tested (Supplementary Figure 7). We therefore applied this approach across all runs using the CoV from the Nigeria simulations and the additional 40 administrative 1 units to obtain 95% uncertainty intervals across the results for SSA.

Results are highly sensitive to when mass LLIN campaigns are scheduled to occur. Multiple countries have sub-national campaigns and it is unclear where within the country LLINs are due to be distributed. To illustrate this uncertainty caused by the timing of LLIN campaigns we conducted a sensitivity analysis for countries where the location of mass campaigns are unknown by simulating distributions in either in 2019 or 2020 (Supplementary Table 12).

SMC was assumed to be undertaken in the same administrative units covered in 2019 and 70% of children under 5 years of age are assumed treated, except in Senegal where children up to ten years old are covered and we assume 70% coverage[15]. We simulated amodiaquine plus sulfadoxine-pyrimethamine as the prophylactic drug delivered for SMC campaigns across three or four rounds depending on the existing strategy of the country[24]. The

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proportion of clinical cases of malaria receiving the appropriate prompt treatment outside the COVID-19 epidemic was estimated based on data extracted from the Demographic and Health Surveys (DHS) on the proportion of febrile children who were given medical treatment, and the type of treatment administered (Demographic and Health Surveys, https://dhsprogram.com/ (accessed September 10, 2018)). Prior to 1 May 2020, indoor residual spraying was assumed to take place annually in the same administrative units covered historically (as per 2018)[25]. During the period of health system interruption SMC and clinical treatment of cases can either reduce to zero, reduce to 50% of the planned level (35% of the target age group are covered for SMC), or continue as before. Indoor residual spraying of insecticide (IRS) is assumed to be cancelled.

The distribution of drugs either through existing SMC channels or through special mass drug administration (MDA) projects could be used to reduce the impact of COVID-19 on malaria. Bespoke methods of delivery are being considered to deliver drugs to households whilst maintaining social distancing. In regions where SMC is carried out, this intervention could be extended from the current target age of children under 5 years old to targeting children under 10 or 15 years. All other aspects of the SMC campaigns are assumed to remain the same (i.e. regions where it is deployed, seasonal timing, number of rounds and coverage within the targeted age group). Outside of regions with SMC, a single round of MDA using a drug with a similar profile of prophylactic protection to sulfadoxine-pyrimethamine plus amodiaquine (in the absence of resistance) is considered. It is assumed to be administered to 70% of the population (either under 5 years of age or to all ages) with the timing of the MDA aligned for each region to be optimally deployed at the start of the peak transmission season.

We simulated the number of malaria deaths from 1 May 2020 to 30 April 2021, for both the non-COVID-19 scenario, and the four COVID-19 scenarios, and for a range of malaria intervention combination strategies. Projected deaths were aggregated across regions and presented as the increase in deaths predicted for the different COVID-19 and malaria scenarios relative to the non-COVID-19 scenario for the year. Sub-national differences outside Nigeria should be treated with caution. Many countries now have mass LLIN campaigns staggered over multiple years for logistical and financial reasons, and this information on sub-national timing of LLIN campaigns were unavailable for all countries other than Nigeria which can introduce substantial uncertainty (Supplementary Table 12). Similarly, at a local level, the impact of service disruption would be greater for clinical treatment where clinics treat a high proportion of the local community relative to clinics serving a proportionally lower sample of the community.

The impact of the uncertainty in the R0 for COVID-19 in Africa on malaria mortality is investigated for Nigeria by assuming the period of service interruption increases from 6 to 9 months which is predicted to be required if the COVID-19 R0 reduced from 3.0 to 2.5 (Supplementary Table 6).

Fever in COVID-19 and malaria

A literature search was conducted to obtain the proportion of fever in COVID-19-positive patients, broken down by age and type of cohort. The search terms “covid” OR “SARS-

CoV-2" AND "fever" were used in the PubMed and MEDLINE (Ovid) databases, yielding 384 non-duplicate records. Titles and abstracts of these records were screened for the words "child" or "children", resulting in 28 hits.

Nine of the 28 papers were systematic reviews, which were screened for further references. With this, 36 papers were added for extraction. In all, 64 full texts were screened. Eight papers were rejected as they were in Chinese (n = 5) or because they did not provide a breakdown of fever between adults and children (n = 3). Data were extracted from 47 papers for this analysis (Supplementary Data 1). Each study examines a different cohort of patients which may influence the prevalence of fever. Here we classify each cohort into those patients admitted to (i) hospital, (ii) intensive care units (ICU), (iii) contacts of known cases, or (iv) a mixed cohort.

Logistic regression is used to characterise how age influences the prevalence of fever in patients confirmed with COVID-19. The reporting of fever increased significantly with age (likelihood ratio test $p<0.01$), though there was no significant difference between the various cohorts examined here (however, the number of data points investigating the presence of fever in contacts of known COVID-19 cases, which is more likely to represent community transmission, were relatively low, Figure 3A). The percentage of people with malarial fever and how this varies with age is estimated from our malaria transmission dynamics model. Results of both models are then combined assuming the prevalence of the two diseases are independent. The malaria model is also used to estimate the proportion of patent infections which are asymptomatic to determine the prevalence of asymptomatic malaria cases in COVID-19 infected individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

All data used in this study are from publicly accessible sources and the results generated are available from the corresponding author on reasonable request.

Code availability

Full details of the COVID-19 and malaria models, their code and parameterisation are freely available at https://github.com/mrc-ide/squire and https://github.com/jamiegriffin/Malaria_simulation, respectively (accessed April 22, 2020).

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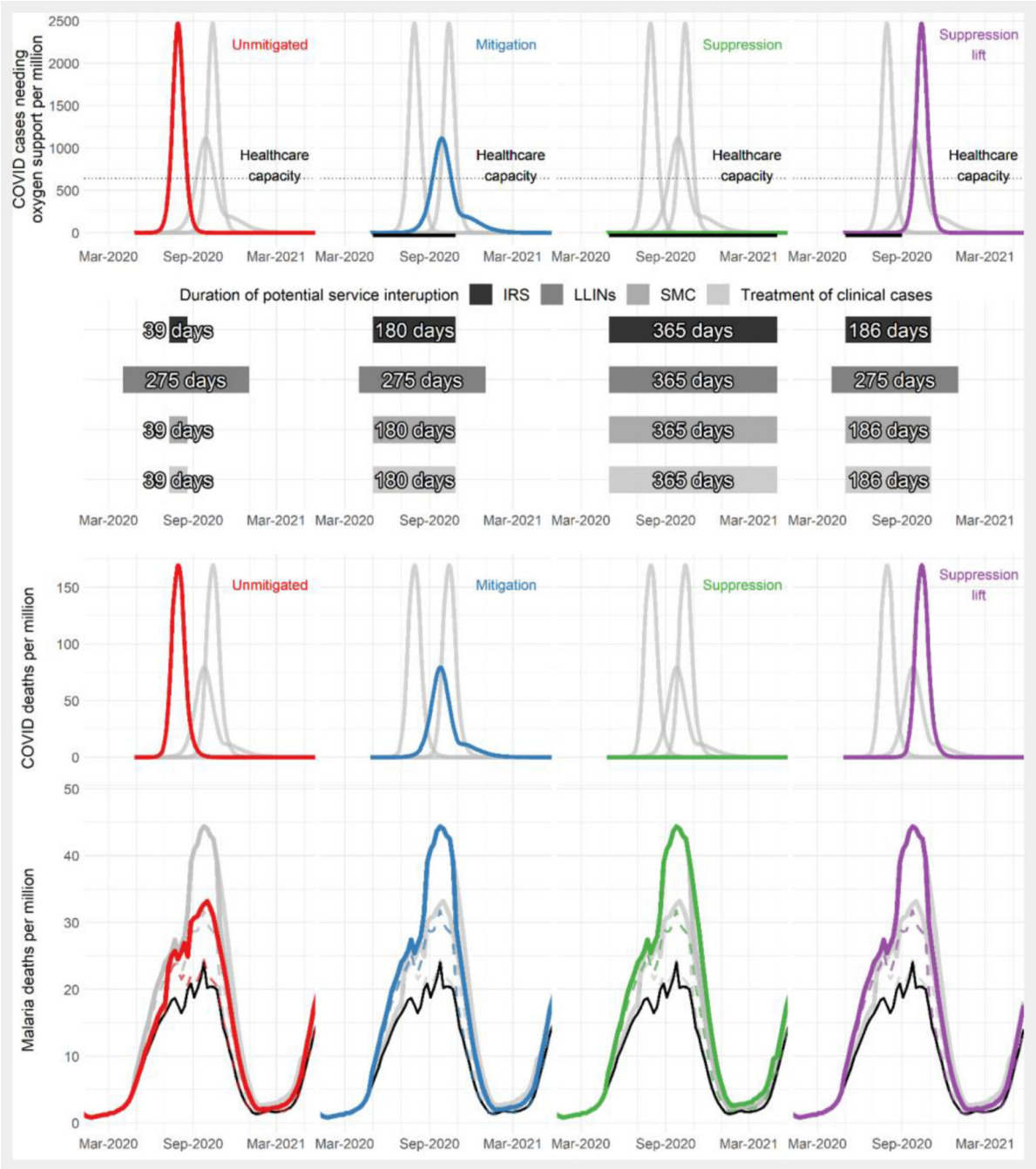

Figure 1. Projected deaths due to COVID-19 and malaria in Nigeria over time for different COVID-19 scenarios.

The top row shows the COVID-19 epidemic and the number of people needing oxygen support per week for four different COVID-19 scenarios − an unmitigated epidemic (where contact rates are reduced by only 20%, red lines in 1st column), mitigation (contact rates are reduced and slow transmission but insufficiently to prevent an epidemic, blue lines in 2nd column), continued suppression (contact rates reduced low enough that numbers of deaths fall and are kept low for 12 months, green lines in 3rd column) and suppression lift (same as suppression but restrictions lifted after 2 months, purple lines in righthand

column). The thin dotted horizontal grey line indicates estimated healthcare capacity for a typical African country. The thick black horizontal line beneath each figure shows the period when COVID-19 mitigation or suppression activities are assumed in operation. The upper middle row indicates the assumed duration of interruption where COVID-19 interventions affect different malaria prevention activities (IRS = indoor residual spraying, LLINs = mass distribution of long-lasting insecticide treated nets, SMC = seasonal malaria chemoprevention) or case management of clinical cases with the level of this disruption presented in Table 1. The lower middle row shows the predicted deaths due to COVID-19 per week in each scenario. The bottom row shows predicted malaria deaths per week for each scenario (coloured lines) and for the counter-factual where there was no COVID-19 induced disruption (black lines). The top coloured lines indicate a scenario where nets and SMC are ceased and case management reduced by half (Supplementary Table 3, row 1) whereas the bottom dashed coloured lines show the most well-managed scenario (Supplementary Table 3, row 3). The mitigation and suppression lift scenarios are predicted to produce very similar malaria epidemics due to the similar periods of service disruption. Grey lines in all rows show other scenario predictions to allow direct comparison. Most malaria cases occur in the latter half of the year because transmission peaks in Nigeria. This makes the differences between the mitigation and suppression scenarios less substantial than seen in sub-Saharan Africa as a whole as transmission is more perennial and East African transmission peaks are earlier in the year (Supplementary Figure 1).

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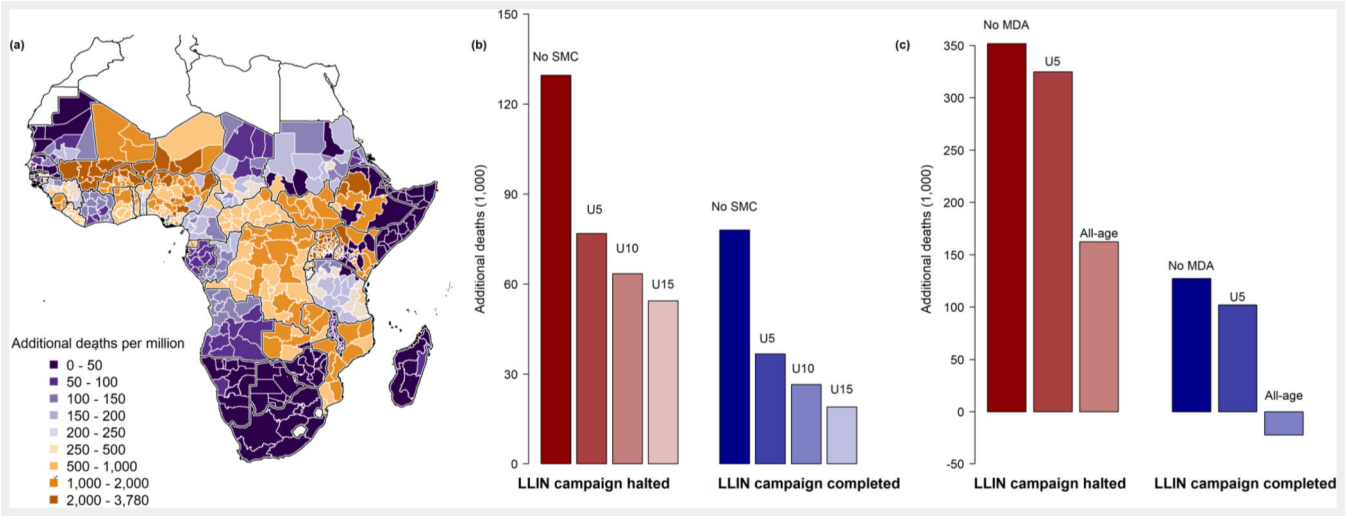

Figure 2. Number of additional deaths due to malaria in different regions of sub-Saharan Africa (SSA) and the impact of expanding existing seasonal malaria chemoprevention (SMC) and mass drug administration (MDA) in a COVID-19 mitigation scenario.

(a) Estimated additional deaths per million people when all malaria interventions (LLIN campaigns, SMC and clinical treatment of cases) are ceased for 6 months relative to normal service in the absence of COVID-19 for each administrative region (maps for other COVID-19 scenarios are presented in Supplementary Figure 2). (b) Reduction in additional malaria deaths by expanding the age of those eligible for SMC in regions within the Sahel where it was conducted in 2019 relative to all malaria interventions cancelled (Table 1, row 11: red bars) or LLIN distributions continue whilst clinical treatment ceases (Table 1, row 8: blue bars). Absolute values are shown in Supplementary Table 7. (c) Reduction in additional malaria deaths by introducing a single round of MDA (using the prophylactic with a similar profile to Amodiaquine plus sulfadoxine-pyrimethamine) for regions where SMC is not currently conducted (Supplementary Table 9). MDA is assumed implemented at the optimal time, prior to the transmission peak for each administration unit. In both SMC and MDA scenarios, we assume that 70% of the respective populations receive the intervention. Negative values indicate there are fewer malaria deaths than would have been predicted if routine antimalarial interventions had been maintained without a COVID-19 epidemic.

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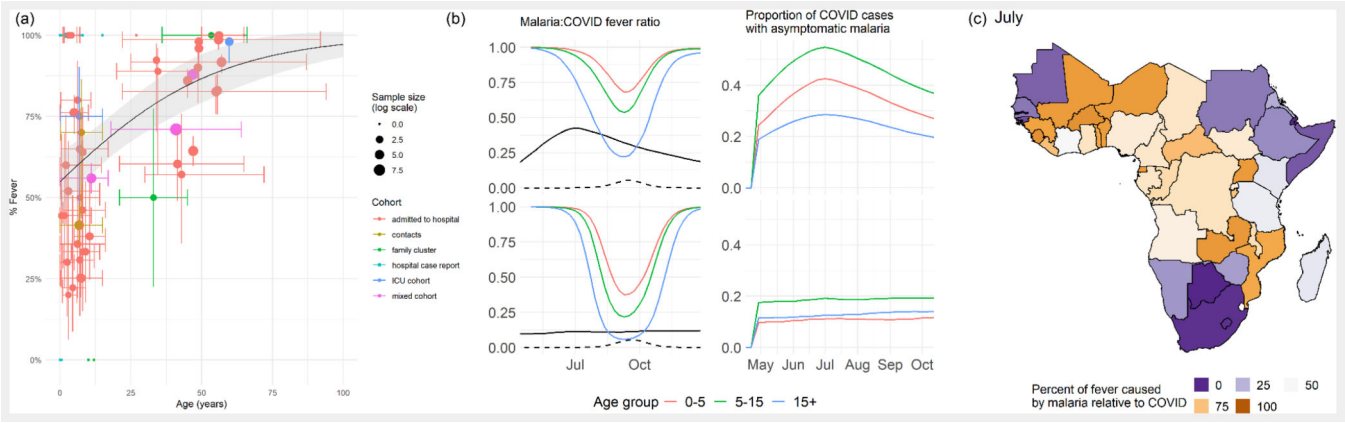

Figure 3. How fever symptoms of COVID-19 and malaria may influence diagnoses.

(a) A systematic review of the literature showing how the percentage of COVID-19 cases with fever varies with respect to age. Points show published estimates coloured according to the cohort they were observed in: patients admitted to hospital (red), intensive care units (ICU, green), contacts of known cases (blue) or a mixed cohort (purple). Solid line shows best fit regression line fit to all groups, shaded region indicates 95% confidence interval estimates in the mean. (b) Left column figures show estimates of how the proportion of malaria fevers relative to COVID-19 fevers (i.e. proportion of fevers due to malaria divided by malaria plus COVID-19 fevers) varies over time whilst right column shows the proportion of COVID-19 cases which are co-infected with asymptomatic malaria. Top row shows predictions for seasonal Mali whilst bottom row shows more perennial Uganda. In all panels in (b), black lines indicate prevalence of malaria (as detected by microscopy), and dashed lines show COVID-19 prevalence; coloured lines indicate age of group in years, either 0−5 (red), 5−15 (green) or greater than 15 (blue) years of age (scaling COVID-19 fevers by age using the regression line presented in (a)). Panel (c) shows country-level mean estimates of the fraction of fevers due to malaria compared to those due to malaria and or Covid-19 in children under 5 years in July 2020. The percentage of children with fever are likely to be over-estimated here as these data primarily come from hospital settings where fever will be more common than the general community and so a greater percentage of fevers in children will be due to malaria.

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Table 1

Projected COVID-19 and additional malaria deaths between 1 May 2020 and 30 April 2021 for different COVID-19 scenarios in malaria-endemic countries in sub-Saharan Africa.

Different combinations of malaria interventions are considered on each row, with the colour denoting whether they were halted for the period of health system interruption (red), reduced to 50% of the normal coverage level (light green) or continued as normal (dark green). *LLINs* = distribution of long-lasting insecticide treated nets in countries due for mass campaigns in 2020, SMC = seasonal malaria chemoprevention in SMC target areas in the Sahel region and, *Treatment* = treatment of clinical cases. LLINs and SMC campaigns are only disrupted in regions where they were previously planned. Care should be taken when directly comparing the relative impact of different malaria interventions as they vary in their period of disruption (other than in the suppression scenario). All possible treatment options are considered, though some, such as the halting of all case management for a year, are considered unlikely. Malaria scenario numbers correspond to those plotted in Supplementary Figure 1 and Figure 2. The point estimate of deaths due to COVID-19 is from the assumption of an R0 of 3.0, with ranges in brackets showing 95% uncertainty interval (95% UI). Additional malaria deaths are shown as the point estimate and 95% UI rounded to the nearest thousand.

				COVID-19 scenario			
				Unmitigated	Mitigation	Suppression	Suppression lift
Projected COVID-19 deaths (‘000) (95% UI)				7,364 (3,215-14,051)	5,923 (2,892 − 11,028)	0.4 (0.3 - 4.5)	7,374 (3,223.5 − 14,024)
Malaria scenario				Additional malaria deaths (‘000) (95% UI) (compared to a baseline estimate of 422 (95% UI 225−619) deaths in this period without malaria service interruption)			
No.	LLINs	SMC	Treatment				
1				239 (140−337)	379 (221−537)	464 (277−651)	380 (222−539)
2				221 (131−312)	282 (167−397)	322 (195−450)	282 (167−397)
3				26 (15−38)	112 (61−163)	200 (115−285)	112 (61−164)
4				39 (21−57)	184 (98−270)	314 (175−453)	186 (99−272)
5				41 (23−58)	129 (71−186)	189 (107−270)	130 (71−188)
6				220 (128−311)	357 (207−507)	495 (296−693)	358 (207−509)
7				25 (13−37)	164 (86−241)	310 (174−446)	165 (87−243)
8				55 (30−79)	205 (110−300)	336 (189−484)	207 (111−302)
9				238 (139−337)	461 (263−659)	696 (413−979)	464 (265−662)
10				219 (127−311)	434 (247−622)	668 (396−940)	437 (249−625)
11				253 (148−357)	481 (277−686)	695 (413−978)	484 (278−690)