Assembling a geo-coded repository of malaria infection prevalence survey data in Africa 1900-2014

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Contents

Pre-amble

This working paper serves as a documentation of how the INFORM project has identified, assembled and geo-coded malaria prevalence data from across Africa and why these data are important to monitor the temporal impact of interventions [1,2].

We focus on *Plasmodium falciparum*, by far the most ubiquitous and pathogenic of the human malarias in Africa, however we have included in our data searches and extractions information, where available, on the prevalence of *P. vivax*, *P. malariae* and *P. ovale*.

The inventories of data cover a long legacy of malaria surveillance in Africa and we describe in this report how we have tried to capture historical and contemporary data. For country-level analysis, undertaken in support of national governments by the INFORM project, data from 1980 is most relevant.

This project has been managed from Kenya for over 10 years but is pre-dated by even earlier efforts undertaken as part of the MARA/ARMA collaboration that began in 1996 [3-5]. The success of the last 20 years of data assembly would not have been possible without the enormous contributions made by many malaria scientists across Africa and all are acknowledged at the end of this report.

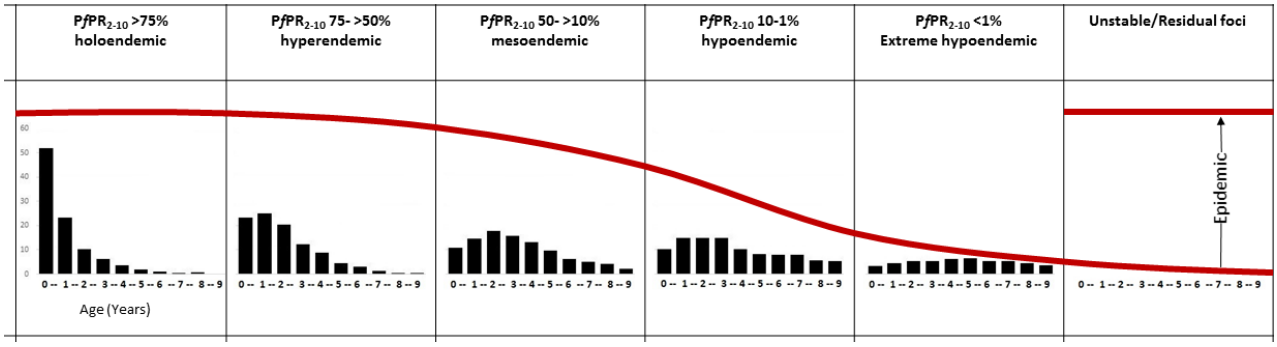
1. Why measure malaria transmission?

There are several reasons why understanding the frequency of human malaria parasite exposure is important for control planning and disease management.

The incidence of disease, and associated clinical phenotypes, depend upon an individual's level of previously acquired functional immunity, which is largely defined by the frequency of new infections experienced from birth [6-12]. In areas where the intensity of malaria transmission is high, most severe disease events are concentrated in very young children and severe outcomes following infection are rare in older children and adults. As the intensity of parasite exposure declines, the clinical burden of malaria is borne by older children until a point when the likelihood of developing a disease event is more proportional to the chances of being infected (Figure 1). Under these conditions the burden of malaria is shared equally across most age groups and the lack of any functional immunity in a community makes populations prone to epidemics (Figure 1).

The changing age-pattern of disease is accompanied by a changing pattern of severe disease presentation. Under intense transmission conditions, severe anaemia is a major cause of life-threatening illness, whereas presentations that include cerebral malaria become increasingly common among communities exposed to moderate-to-low levels of transmission intensity [7,9,11].

Figure 1: Conceptual framework of the clinical epidemiology of *Plasmodium falciparum* under declining parasite transmission intensity in Africa [Snow, 2015]. The red line represents a theoretical rate of severe disease and mortality incidence and the black bars are the proportional distribution of severe malaria between birth and the 10th birthday based on previously published work [7,9]



Mechanistic, biological models that reproduce the mathematical properties of malaria transmission, predict that the likely impact of different drug or insecticide-based strategies of malaria control will have different overall effect size and duration of intervention required to demonstrate impact, depending on the levels of starting endemicity [13-18].

In broad terms reducing man-vector contact, through for example the use of insecticide-treated bed nets (ITN), alone will never interrupt transmission in areas of very intense transmission. Conversely if used by 90% of the population 100% of the time in areas of intermediate transmission, ITN alone might reduce parasite exposure to almost zero within eight years [14-15].

Adjunct vector control measures are required to supplement ITN strategies in areas of intense malaria transmission to rapidly reduce vector abundance enough to have a sustained impact on transmission [15]. The predicted immediacy and overall impact on transmission of mass-drug administration (MDA) and indoor-residual house spraying are also contingent on the intensity of transmission before intervention starts [15-18].

Impacts on transmission through the effective use of currently available artemisinin-based combination therapy (ACT) are greatest in areas where most new clinical infections are treated and the intensity of transmission is low, while the impact of ACT treatment on local transmission is considerably less in areas where the intensity of parasite transmission is high [19] or when used for MDA [18]. To achieve an impact on transmission through routine treatment strategies alone requires different types of drug combinations than those currently used in Africa [19].

The effects of malaria infection among pregnant women has been well described and include the insidious effects of repeated infections on anaemia, increased risks of intrauterine death, low birth weight deliveries leading to higher risks of infant mortality and under conditions of unstable transmission increased risks of maternal death during pregnancy [20,21]. Intermittent Presumptive Treatment (IPTp) with two doses in the second and third trimesters using the long half-life drug sulphadoxine-pyrimethamine (SP) has been implemented across much of sub-Saharan Africa since 2001 [22]. In recent years, this recommendation has, in some countries, been extended to three doses of SP from quickening. As transmission declines the cost-benefit of IPTp changes; while the evidence remains inconclusive when to stop IPTp [23], currently it is suggested that when prevalence in children declines below 5% one might consider either stopping IPTp or introducing screening and treatment for pregnant women [24].

Seasonal malaria chemoprevention (SMC), has been shown to prevent approximately 75% of clinical malaria episodes among children aged less than five years, in areas where transmission is concentrated within a few months of every year [25]. Targeting SMC within national borders depends upon not only knowledge of malaria seasons but also the intrinsic, pre-intervention endemicity risks. In areas where transmission intensity is historically low, but seasonal, the cost-benefits of SMC are minimal compared to areas where parasite prevalence is above 5% [26]. Equally important is an understanding of current levels of malaria transmission that will define the likely age-range most suited to SMC, for example 3 months to the 5^{th} birthday (arbitrarily set at a prevalence above 10%) or, as transmission declines, 3 months to the 10^{th} birthday where prevalence is between 5 and 10% [27].

When transmission intensity declines to low levels, patterns of parasite risk become increasingly more heterogeneous where spatially localized foci of transmission contribute more than 80% of transmission risk across neighbourhoods [28]. While there are no hard and fast rules for when this becomes important for malaria control, it has been suggested that when wider community malaria prevalence falls below 5% [29] more targeted approaches to disease prevention should be adopted [30-32]. States of very low parasite prevalence also serve as signals to control agencies to consider revising control strategies that embrace elimination ambitions [33].

Understanding the intensity of malaria parasite transmission is central to effective planning of control and in defining the clinical phenotypes that require management. Throughout control the intensity of transmission serves as a measureable index of intervention success and a benchmark for programmes to adapt intervention mixes to maximise gains and re-orientate control for pre-elimination.

2. Measuring malaria risk

2.1 Measuring stable, endemic malaria transmission

The rate of parasite exposure can be measured using a variety of epidemiological techniques from detailed vector based measures of human biting rates, proportions of vectors with parasites in their salivary glands, their parity and longevity or in human hosts from longitudinal or cross-sectional studies of parasite acquisition from birth to the first birthday using combinations of parasite detection and serology [34]. Vector-based measures of malaria transmission are important parameters for modelling intervention impact, however are difficult and costly to measure empirically under field conditions [35].

The most commonly measured metric of parasite exposure is the parasite rate (PR) in human hosts (strictly a ratio as it measured at one time point). The PR is the proportion of individuals on a single cross-sectional survey among an entire or sampled community who have evidence of a peripheral blood stage malaria infection. The PR is not a direct measure of transmission as it saturates at high levels of transmission because of heterogeneous biting, multiple infections and acquired immunity. Mathematical models have been developed to translate PR values into values of Entomological Inoculation Rates (EIR) or the basic reproduction rate of infection [28], however in practical terms malaria control programmes use the PR as a direct marker of transmission intensity.

During the Global Malaria Eradication Programme (GMEP) era of the 1950s and 1960s, the prevalence of the malaria parasite in children was viewed as a measurable, definitive index of risk that would define how interventions were spatially targeted, and progress measured [36-41]. Following the conference on malaria in Africa held in Kampala, Uganda in 1950 [42], malaria experts agreed upon a set of classifications of stable malaria endemicity based on the *P. falciparum* infection prevalence in children aged 2-10 years (*Pf*PR_{2-10}) or infants: hypoendemic transmission where *Pf*PR_{2-10} was less than 10%, mesoendemic transmission where *Pf*PR_{2-10} was between 10% and 50%, hyperendemic transmission where *Pf*PR_{2-10} was between 51% and ≤75% and holoendemic transmission where infection prevalence in infants was > 75% [36]. These terms had been in operation before the Kampala conference but largely referred to the less specific prevalence of enlarged spleens in children, rarely used today. Holoendemic transmission is rarely empirically defined among infants and is more usually estimated from age groups used to classify other endemicity classes, as such is usually regarded as a state where *Pf*PR_{2-10} is ≥ 75%. Importantly, these classifications have retained a qualitative value in national descriptions of transmission intensity for over 60 years.

2.2 Measuring risk when prevalence is low and the use of routine case data

Optimizing, and operationalizing, definitions of malaria transmission intensity has recently been reviewed to provide metrics to help decisions on when countries, or regions within countries, might elect to develop an elimination agenda [33]. *Controlled low-endemic* malaria has been suggested as a state where interventions might have reduced the average parasite rate in a nationally representative sample below 1% during the peak transmission season, while prevalence levels in sub-populations remain below a higher threshold (e.g., lower than 5% prevalence) to allow for heterogeneity in endemicity caused by focal transmission. Since the "controlled" component of this definition does not apply to a region in which malaria transmission has historically always been low, this is distinguished from *low-endemic malaria* [33]. As such there are increasing adaptations of the hypoendemic classification to include areas defined by a *Pf*PR_{2-10} of <1% and <5% [2].

There is also a practical sampling consideration when transmission intensity becomes very low, or unstable. Increasingly larger, more repeated community surveys are required to provide estimates with reliable precision. In this transitional state, decisions to abandon community surveys in favour of passive and/or active case-detection or fever infection prevalence surveys should be made. This was defined operationally during the GMEP: "*As soon, however, as the general volume of malaria has been reduced to any considerable extent, the indices furnished by malariometric surveys are no longer sensitive enough to measure further progress ... Analysis of evaluation data from eradication programmes as well as closer observations in the field have shown that the point at which malariometric surveys cease to be sufficiently sensitive is reached when parasite rates have dropped to a level of between 1% and 3%*" [43].

The terms stable and unstable transmission are widely used but rarely quantified. This is an important distinction because a transition to unstable states implies a transition toward elimination. The stable–unstable classification was first introduced into malariology by Sir Ronald Ross [Ross, 1916] and adapted by George Macdonald for the measurement of malaria endemicity where stability was defined quantitatively by the average number of feeds that a mosquito takes on man during its life [39,44]. The stability index, however, demands detailed entomological data that are rarely available. Qualitatively, stable malaria refers to situations that are relatively insensitive to natural and man-made environmental changes. Unstable malaria includes areas very sensitive to climatic aberrations and very amenable to elimination and often prevails in areas of extreme aridity, where abrupt changes in usual rainfall can lead to epidemics.

The enhanced vegetation index (EVI) derived from the MODerate-resolution Imaging Spectroradiometer (MODIS) sensor imagery has been used to delineate areas subject to extreme aridity and thus potentially unstable malaria transmission [2,45-47]. However, the EVI satellite imagery provides a striated visualization of aridity across Mali, Niger and Chad, a function of the quality of the imagery. Despite an illusion of precision for unstable malaria transmission, this has never been validated against empirical data on clinical incidence or prevalence. We have therefore avoided the use of EVI in subsequent definitions of unstable malaria transmission.

A more established definition of "unstable" malaria is based upon case-incidence. The measurement of malaria incidence requires every suspected malaria case to be diagnosed through a comprehensive surveillance system comprising passive case detection (PCD) by parasitological examination of those suspected, usually febrile cases presenting the health service, supplemented by active case detection (ACD), the examination of fever cases sought through household visits at regular intervals [34,40,43,41]. The results are usually expressed as an Annual Parasite Incidence (API) per 1000 of the entire population of the administrative areas for which it is representative. During the GMEP the API was only deemed valid if the annual blood examination rate (ABER), the proportion of the target population examined, exceeded 10% [40,48]. The other metric often presented is the slide positivity rate (SPR). These surveillance indices are related as follows: API = (ABER * SPR) / 10[a] [49].

In recent global [45] and regional [2,47] mapping exercises, there has been a preference for using a very conservative case-incidence value of <1 case per 10,000 population. While this recognizes the difficulties in measuring case-incidence it assumes that case identification through routine systems continues to be as poor as it has been over the last two decades. Health information systems and rates of parasite confirmed cases are improving across Africa and the challenge now is to ensure that the best possible use of this data is made in accordance with WHO accepted definition of pre-elimination being < 1 case per 1000 [17,31,32] population where this can be confidently recorded or partially incomplete data from health systems used by the majority of the population can be effectively spatially modelled.

In many applications for overseas funding, national malaria strategies, or malaria programme reviews, case incidence or case numbers as reported by routine health information systems (HIS) are increasingly being presented in maps across sub-Saharan Africa including: Benin, Botswana, Burkina Faso, Congo, Cote D'Ivoire, Eritrea, Guinea Bissau, Malawi, Mauritania, Mozambique, Sao Tome & Principe, Senegal, Togo, Zanzibar and Zimbabwe [50]. These data are incomplete and do not always reflect parasitologically confirmed cases. Nevertheless these examples highlight the growing appetite in applying routine malaria case data to malaria risk stratification and mapping.

Imperfect and incomplete HIS malaria data has recently been modelled using advanced geo-statistical methods to accommodate facility use, incomplete monthly data and geo-coded locations of health facilities in Namibia [51] and Zambia [52]. These novel approaches to handling incomplete routine data, in combination with scaled diagnostic capacities offers some exciting new opportunities to model case-incidence where most fevers seek treatment in the formal sectors and most fevers are parasitologically confirmed.

For countries, or areas within countries, seeking to achieve elimination in Africa, combinations of PCD and ACD with case investigation have begun in South Africa [53], Swaziland [54], Zanzibar [55], Cape Verde [56] and districts bordering the Senegal River in Senegal [57].

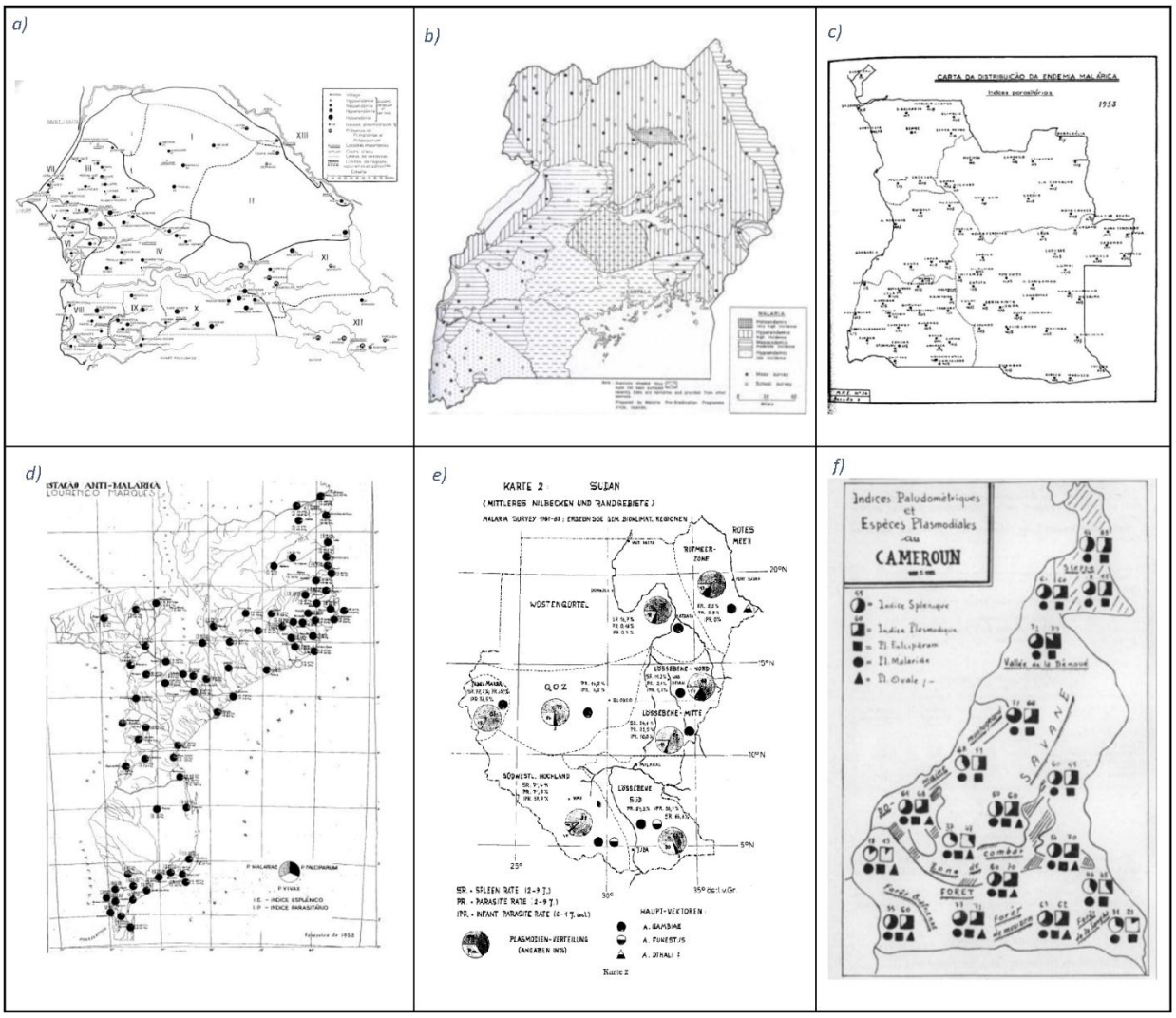
[a] The division by ten is necessary because API is expressed per 1000 and the other terms per 100

The transition from control to pre-elimination is a continuum and metrics used to define these endpoints need to be reflected by combinations of measures depending on the availability and quality of national data. Where reliable health information systems do not exist or where parasite prevalence remains high, it is necessary to use community-based infection prevalence as an indicator of risk. When elimination is a defined end-game, the detection of all infections rather than all disease events becomes a priority. All metrics of risk must be able to stratify geographical regions with adequate precision. These stratifications should link to what is required to move a region further down the continuum toward the ultimate challenge of elimination. There are no definitive guidelines for what can be measured and what criteria are necessary to begin to adapt control strategies. We are working with the WHO to ensure that these have greater clarity in the near future.

3. The history of national parasite surveys in Africa

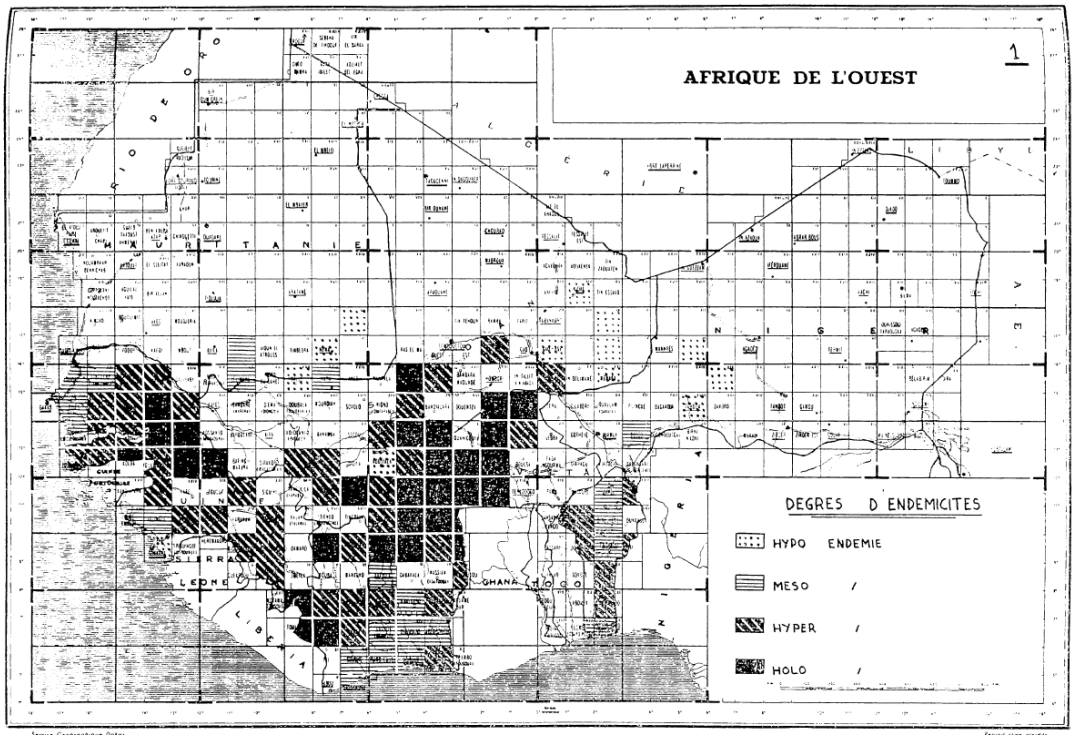
Some of the earliest national surveys of infection prevalence were undertaken in Senegal 1905-1906 [58], Algeria 1908 [59], Ghana 1913 [60], Zanzibar 1923-1926 [61] and Mauritius 1923-1925 [62]. National parasite surveys were recommended across Africa during the preparatory and attack phases of malaria elimination under the GMEP [40,43,48]. These were based on statistical sampling methods to allow for adequate precision of individual community prevalence depending on expected levels of prevalence [63]. Examples of these national surveys span 30 years of preparation for malaria control in Africa including surveys before the Kampala Conference in Egypt 1936 [64], Cape Verde 1946 [65], Liberia 1948 [66] and Namibia 1950 [67]; and after the Kampala Conference in Morocco 1951-1953 [68], Mozambique 1952 [69,70], Madagascar 1952-1953 [71], Angola 1953 [72], Benin 1954 [73], Cameroon 1954 [74], Zimbabwe 1956 [75], Senegal 1960 [76], Sudan 1961-1963 [77], Somalia 1960-1961 [78,79], Botswana 1962 [80,81], Togo 1962-1964 [82], Mauritania 1963-1965 [83,84], Sierra Leone 1963-1966 [85], Algeria 1964-65 [86], Ethiopia 1964-1965 [87,88], Uganda 1965-1967 [89] and Zambia 1969-1972 [90]. Examples of the hand-drawn representations of these national survey data are shown in Figure 2.

Figure 2: Examples of national malaria prevalence surveys during the GMEP era: a) Senegal [76]; b) Uganda [89]; c) Angola [72]; d) Mozambique [70]; e) Sudan [77]; f) Cameroon [74]



The Centre Muraz, based in Bobo Dioullaso in Burkina Faso, was originally the headquarters of the Sub-regional Service Général d'Hygiène et de Prophylaxie (SGHMP), that provided medical and sanitary advice and research for the countries that formed the Federation of French West Africa (Afrique Occidentale Française, AOF). Under the Centre Muraz, massive household surveys were undertaken across the sub-region to establish the prevalence of Yaws and syphilis in 1955. The head of the malaria section, Commander Doctor Choumara, suggested that it would be of no extra cost to include complementary surveys on malaria, without specially delaying the work of the Treponematoses team. Over the next few years, the very first sub-regional maps of empirical malaria prevalence were developed [91] (Figure 3).

Figure 3: Results of sub-regional malariometric surveys conducted as part of Treponeme investigations in mid- to late 1950s by Centre Muraz across AOF [91].



During elimination efforts a number of countries maintained wide-area community-based parasitological surveys, however for the majority of countries in sub-Saharan Africa, national household surveys of malaria infection were abandoned.

In 2005, five years after the launch of the Roll Back Malaria (RBM) initiative, there was a recognition that it was important to resurrect national household surveys of infection prevalence as a means to monitor country-level progress [92,93]. The three principal survey vehicles for contemporary national parasite prevalence data have been the Demographic and Health Survey malaria modules, managed by the US based MEASURE-ICF programme [94], Multiple Indicator Cluster Surveys, managed by UNICEF [95] and standalone Malaria Indicator Surveys (MIS) managed by national malaria control programmes and their survey partners. These surveys are developed with a focus on tracking changes in intervention coverage and under five-mortality at the first level administrative areas (Province, State, Governorate etc). Stratified, population-weighted national sampling is not based on precision around malaria prevalence, one consequence is that the resulting primary sampling units have very small numbers of individuals sampled for malaria infection. This is an important distinction between those national malaria surveys undertaken during the GMEP era that were designed around the power to define infection prevalence [63].

Current national surveys include combinations of methods parasite detection in different age groups depending on the national survey. The majority, however, focus only on children aged 6

months to five years, a less informative age group for infection prevalence than those surveys that include a much wider childhood age range [96] and a further departure from the national surveys of the 1950s and 1960s which either focussed on children under 10 or under 15 years of age or considered all household members.

Despite these limitations there has been a large increase in empirical data on malaria infection prevalence across Africa, not available across such a wide geographical range for over 40 years. Since 2006 national malaria parasite surveys have been undertaken in Angola (2006 and 2011), Botswana (2012), Benin (2012), Burkina Faso (2010 and 2014), Burundi (2012), Cameroon (2011), Chad (2011[b]), Comoros (2010[b]), Cote D'Ivoire (2012), Democratic Republic of Congo (DRC) (2009 and 2013/14), Djibouti (2009[b]), Equatorial Guinea (2007 and 2010/11[b]), Eritrea (2002 and 2012[b]), Ethiopia (2006, 2007 and 2011[b]), Gabon (2007, adults only[b]), The Gambia (2008[b], 2010[b] and 2013), Ghana (2011), Guinea (2012 and 2014/15), Guinea Bissau (2008/09[b]), Kenya (2007[b] and 2010[b]), Liberia (2009 and 2011), Madagascar (2011 and 2013), Malawi (2000, 2009, 2012 and 2014), Mali (2010), Mozambique (2002[a], 2007[a] and 2011), Namibia (2009[a]), Nigeria (2010), Rwanda (2007 and 2010/11), Senegal (2008/9, 2010/11, 2012/13 and 2013/14), Sierra Leone (2013), Somalia (2005[b] and 2014[b]), South Sudan (2009[b] and 2013[b]), Sudan (2005[b], 2009[b] and 2012[b]), Swaziland (2010[b]), Tanzania (2007/8 and 2011/12), Togo (2013/14), Uganda (2009 and 2014/15), Zambia (2006[b], 2008[b], 2010[b] and 2012[a]), Zanzibar (2007, 2010 and 2011/12) and Zimbabwe (2009 and 2012).

With a growth in community based surveys of infection prevalence, there has been a renaissance in surveys of school children. This age group provides a more optimal range for the investigation of infection prevalence and where school attendance is high, and transmission intensity is stable, this approach to measuring community parasite exposure is less expensive and labour intensive than community based sampling [97,98]. The use of infection prevalence in school children to track the progress and impact of malaria control and elimination is not new. School surveys were undertaken as part of surveillance in Southern Rhodesia (now Zimbabwe) [75]; Bechuanaland (now Republic of Botswana) [80], Uganda [99,100], Mauritius [62] and Sierra Leone [101]. In Kenya, school malaria surveys were routinely done for malaria surveillance by the Division of Vector Borne diseases (DVBD) since its establishment in 1940s through to the early 1990s when they were abandoned due to lack of funds [DVBD, unpublished data]. Recent, national school-based surveys have been resurrected in Kenya [102,103], Côte d'Ivoire [104], Ethiopia [105], The Gambia [106], Mali [107], Tanzania [F Molteni, personal communication], Mozambique and Malawi [Natalie Roschnik, personal communication] and Uganda [108].

Co-sampling during broader health surveys was first proposed in the 1950s for treponemes and malaria [91] and during nutritional surveys in Zambia [90]. Recently the opportunities shared by including malaria surveys in other health surveys has been re-visited, notably screening for neglected tropical diseases [109] or nutritional surveys offer opportunities to include malaria testing. In Somalia, for example, we have worked with the Food Security and Nutrition Analysis Unit (FSNAU) of the Food & Agriculture Organisation in Somalia to include malaria rapid diagnostic tests during community nutritional screen between 2007 and 2011 [110].

[b] Data made available to INFORM team by national malaria control programmes without permission for third party distribution

4. Assembling parasite prevalence survey data

As highlighted above, there have been two major waves of interest in national surveys of parasite prevalence, both around global initiatives to control and eliminate malaria led by the WHO. However, there have been numerous sub-national and individual site investigations of malaria infection prevalence across the continent since the early 1900s. Identifying these survey data has been a long and arduous process, taking over *circa* 20 years. This section describes the process, data extraction and completeness of this data search.

4.1 Background to data search strategies

The basic principles of searching for information on malaria infection prevalence in Africa were established under the Mapping Malaria Risk in Africa/Atlas du Risqué de la Malaria en Afrique (MARA/ARMA) collaboration [4] and extended in 2005 under the Malaria Atlas Project (MAP) [Guerra et al., 2007]. Both of these provisional data assembly projects highlight one important aspect of locating malariometric information in Africa, the majority of data come from unpublished sources. This would not have surprised malariologists working in Africa over fifty years ago. Bagster-Wilson states in Boyd's treatise on malaria in 1948 that "*An attempt may be made to define with more precision the distribution of malaria so far as available information will permit……much local knowledge is hidden in unpublished official reports which cannot be consulted except by visits to the countries concerned*" [111].

Methods used by us to identify sources of information have been opportunistic, cascaded approaches and do not adhere to stick methods proposed for systematic reviews or meta-analysis [112] as a reliance only upon peer-reviewed materials would result in the exclusion of valuable, rich data sources at country-levels. We have used personal contacts, casual references to surveys in ministry of health reports, searches of archives and more traditional peer-reviewed publication searches to track down possible sources of malaria survey data from across the continent. The following sections attempt to articulate the approaches taken to locate information.

4.2 Historical archive searches

Since 2005, we have undertaken manual searches of the archives and libraries of ex-colonial tropical medicine institutes to locate unpublished reports from malariologists working in Africa before countries achieved independence. These included archives at the Institute of Tropical Medicine, Antwerp; Institute Pasteur, Paris; Department of History of Medicine, Sapienza - Università di Roma, Rome; ArchivioItaliano Di Scienze Mediche Coloniali, Rome; Instituto Higiene Medicina Tropical, Lisbon; The Wellcome Trust Library, London; The National Archives, Kew, UK; and the London School of Tropical Medicine and Hygiene, London.

Of particular note have been consultant's trip reports and quarterly reports from malariologists working on behalf of the World Health Organization (WHO) from the 1950s through to the 1970s. These provide rich narratives and survey data from pre-elimination campaigns, elimination progress reports, reviews and national malaria situation analyses, all archived at the WHO libraries

in Geneva, Cairo and Brazzaville (Figure 4). We are grateful to the librarians of these archives who provided invaluable assistance in locating unpublished materials in each of these WHO headquarters.

Figure 4: World Health Organization archives in Geneva (left) and Brazzaville (right)

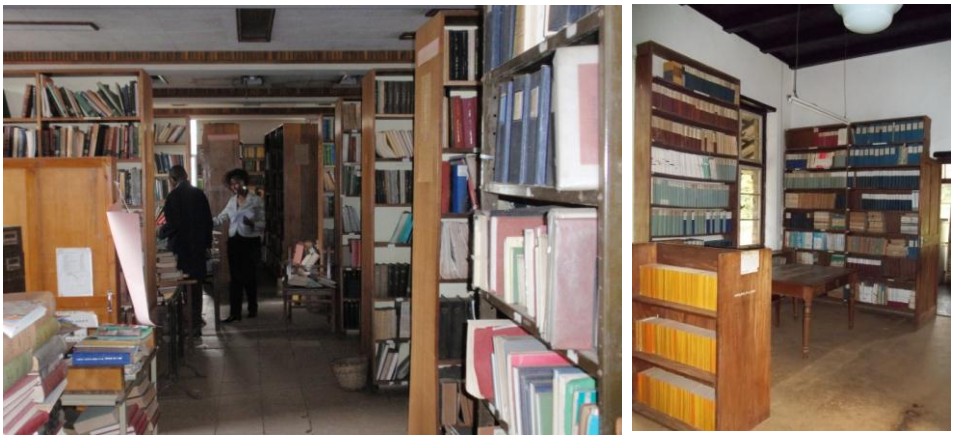
We also visited national archives of the Ministry of Health offices at Nairobi, Kisumu, Eldoret, Mombasa and Meru (Kenya), Entebbe and Jinja (Uganda), Sennar, Khartoum and Kassala (Sudan), Thies (Senegal), Amani (Tanzania), Accra (Ghana), Tzaneen (South Africa) and the personal archives of the ex-director of Tzaneen Malaria Research centre (covering South Africa, Namibia and Botswana). Records and reports held at the National Institute of Medical Research in Amani (Figure 5) covered the period when the centre was the sub-regional, East African Institute of Malaria and Vector Borne Diseases (1954-1977). The eradication headquarters at Jinja, Uganda, housed all the national household survey records from the 1960s, until 2011 when they were unfortunately destroyed and we were able to locate only those that had been re-located to Entebbe.

Annual medical and sanitation department reports from 1919 produced by the Colonial governments of The Gambia, Nigeria, Gold Coast (Ghana), Sierra Leone, Somaliland, Kenya, Tanganyika (Tanzania), Zanzibar, Uganda, Belgian Congo (DRC), Bechuanaland (Botswana), Nyasaland (Malawi), Rhodesia (Zambia and Zimbabwe), Mauritius and Sudan were available in variable states of preservation, in the library founded by the Wellcome Trust in 1963 and now part of the National Public Health Laboratories of the Ministry of Health, Nairobi, Kenya (Figure 5).

During the Mapping Malaria Risk in Africa (MARA/ARMA) collaboration regional scientists visited national archives in Maputo (Mozambique), Bobo Dioulasso (Burkina Faso), Yaoundé (Cameroon), Cotonou (Benin) and Lome (Togo) [MARA/ARMA, 1998]. These searches identified several important reports of national survey data. Digital copies of original reports were however not taken. Where possible we have attempted to re-locate these reports and make digital copies. This has not been universally successful and therefore we have included some pre-independence survey data from the MARA/ARMA database with accompanying citations, most notably those

retrieved originally from the Centre Muraz in Bobo Dioulasso. Unpublished digital copies of reports from European and African archives are made available to countries under the INFORM project as digital libraries.

Figure 5: Left National Public Health Laboratory Archives, Nairobi, Kenya (Old Wellcome Trust Library); Right National Institutes of Medical Research Library, Amani, Tanzania



4.3 Electronic data searches

Online electronic databases were used as one means of identifying peer-reviewed, published data on malaria infection prevalence, most notably those published since the 1980s, including: PubMed [113]; Google Scholar [114]; the Armed Forces Pest Management Board – Literature Retrieval System [116]; the World Health Organization Library Database [116]; and the Institute de Recherché pour le Development on-line digital library service [117].

Regional journals, including the large number of national medical, public health and parasitological journals, were not identified readily from the above sources but titles and abstracts were available on African Journals Online (AJOL) [118].

In all digital electronic database searches for published work the free text keywords "*malaria*" and "*country-name*" were used. We avoided using specialised Medical Subject Headings (MeSH) terms in digital archive searches to ensure as wide as possible search inclusion. Database searches were undertaken at least once per year from 2005.

Searches were supplemented through routine weekly notifications from Malaria World [119], the Roll Back Malaria news alert service, the Environmental Health at USAID malaria bulletins [120] and Santé Tropicale for Francophone country national and regional journals including Medecine D'Afrique Noire [121].

Titles and abstracts were used to identify possible parasite cross-sectional survey data in a variety of forms: either as community surveys, school surveys, other parasite screening methods or

intervention trials. We also investigated studies of the prevalence of conditions associated with malaria when presented as part of investigations of anaemia, haemoglobinopathies, blood transfusion or nutritional status to identify coincidental reporting of malaria prevalence. In addition, it was common practice during early anti-malarial drug sensitivity protocols to screen community members or school attendees to recruit infected individuals into post-treatment follow-up surveys, often data from the survey sites selected present the numbers screened and positive. Surveys of febrile populations or those attending clinics were excluded.

Publications with titles or abstracts suggestive of possible parasite data were either downloaded from journal archives where these have been made Open Access (OA) or sourced from HINARI [122]. If publications were not available OA from HINARI we visited UK library archives at the London School of Hygiene and Tropical Medicine, the Liverpool School of Tropical Medicine, the Bodleian library at the University of Oxford or the Library at the Institute Pasteur, Paris to obtain copies. References not found following these searches were requested using world catalogue searches through the Oxford libraries at a per-page cost.

All publications from which data were extracted were cross-referenced using the bibliographies for additional sources that may have been missed or that may correspond to unpublished or 'grey' literature, not controlled by commercial publishers. Authors of peer-reviewed papers were often contacted to enquire about additional information within their paper and directions to other possible unpublished work in their geographic area or from their institution.

4.4 Other data sources

National household sample surveys that have included parasite prevalence have been described in Section 3. Data from these surveys are either available in downloadable formats from the ICF Measure programme or have been provided to the INFORM project by national malaria control programmes as part of collaborative agreements. For other possible unpublished, site-specific data on malaria prevalence we reviewed web-sites and contacted Non-Governmental Organizations (NGO) working across Africa who may have undertaken health assessments that included parasitological investigations of communities where they worked. These included Médecins sans Frontières [123], MERLIN [124], the Carter Center [125], The Food Security and Nutrition Analysis Unit - Somalia (FSNAU) [126], Shape Consulting [127], Save The Children [128], the Malaria Consortium [129] and MENTOR [130]. Contacts through these agencies led to identification of data from sites in Guinea, Sierra Leone, Côte d'Ivoire, Tanzania, Liberia, Somalia, Kenya, Uganda, Nigeria, Ethiopia, Mali and South Sudan.

Tropical Medicine and malaria meeting abstract books were identified from as many sources as possible produced as part of national and international conferences and congresses. These were used to signal possible data that were followed up through correspondence with abstract authors.

Our regional presence and connections to the wider African malaria research community has created an awareness of the purpose and ambition of malaria mapping research first started in 1996 under the MARA/ARMA collaboration [3,5]. This regional connectivity of research scientists

was used to directly contact colleagues working on the epidemiology of malaria to seek disaggregated site-specific and often unpublished data. The willingness to share unpublished parasite survey data has been unprecedented, by 1st July 2015 over 700 individual scientists and public health specialists have contributed disaggregated information on published data, unpublished data or have assisted in the location of sampled communities across Africa, all are acknowledged in the accompanying Annex and on the INFORM website [131].

Most notable in helping provide unpublished data have been the regional malaria research institutes and their collaborating partners including: The Medical Research Council Laboratories (The Gambia), the Kenyan Medical Research Institute collaborative partnerships with the Wellcome Trust/University of Oxford, US Centers for Disease Control, Nagasaki University and Walter Reed (Kenya), the Malaria Research Training Centre (Mali), Uganda Malaria Surveillance Project (Uganda), Ifakara Health Institute's collaborative partnerships with the Swiss Tropical Institute, London School of Hygiene and Tropical Medicine and US Centers for Disease Control (Tanzania), Dar es Salaam Urban Malaria Control Project (Tanzania), National Medical Research Institute at Amani (Tanzania), Institut Pasteur (Madagascar),L'Institut de Recherche pour le développement (Senegal), Centre de Recherché en Santé de Nouna (Burkina Faso), Institute for Endemic Diseases, University of Khartoum (Sudan), Blue Nile Health Project-Giezera State University (Sudan), Centro Investigaco Saude Angola (Angola), Liverpool School of Tropical Medicine, Wellcome Trust and College of Medicine, University of Malawi collaborative programme (Malawi), South African Medical Research Council (South Africa, Mozambique and Swaziland), Swiss Tropical and Public Health Institute's collaborative programme (Côte D'Ivoire), US Centers for Disease Control collaborative programme (Togo), Prince Leopold Institute's country level collaborative partnerships (Burundi, Benin and Rwanda), Malaria Institute at Macha (Zambia), Medical Research Centre/Uganda Virus Research Institute (Uganda) and the Southern African Malaria Consortium (Zimbabwe).

5. Survey data abstraction

5.1 Minimum data requirements

From each of the survey reports the minimum required data fields for each record were: description of the study area (name, administrative divisions and geographical coordinates, if available), the dates of start and end of the survey (month and year) and information about blood examination (number of individuals tested, number positive for *Plasmodium* infections by species), the methods used to detect infection (microscopy, Rapid Diagnostic Tests (RDTs), Polymerase Chain Reaction (PCR) or combinations) and the lowest and highest age in the surveyed population.

For data derived from randomized controlled intervention trials, data were only selected when described for baseline, pre-intervention and subsequent follow-up cross-sectional surveys among control populations. When cohorts of individuals were surveyed repeatedly in time we endeavoured to include only the first survey and subsequent surveys if these were separated by at least five months from the initial survey to avoid dependence between observations based on

treatment of preceding infected individuals. If it was not possible to disaggregate repeat surveys these were finally excluded from the analysis.

Several countries maintained mass-blood surveys after they had reached consolidation phases of elimination. The duration of the pre-elimination, attack, consolidation and maintenance phases of elimination varied between countries [47]. We have chosen to exclude data that were sampled after dates that eliminating countries had begun to use case-incidence derived annual parasite index or where mass blood surveys were used to prove absence of transmission in Algeria (1967), Egypt (1965), Libya (1967), Mauritius (1957), Morocco (1969), Reunion (1953) and Tunisia (1968).

Occasionally, reports presented the total numbers of people examined across a number of villages and only the percentage positive per village; here we assumed the denominator per village to be equivalent to the total examined divided by the total number of villages. It was possible to establish the year of every survey; however, the month of survey was occasionally not possible to define from the survey report. Here we used descriptions of "wet" and "dry" season, first or second school term or other information to make an approximation of the month of survey and included a record of this assumption. Some survey results were reported as an aggregate in space (e.g. a single *Pf*PR for a group of villages) or time (e.g. a mean *Pf*PR estimated from four different surveys conducted over time). In such cases we either sought additional reports of the same surveys with higher spatial or temporal resolution. Where this was not possible and where clusters of villages exceeded 5 km^2 we excluded the record from the analysis (see below). Where additional information to provide unique time, village specific data was necessary we contacted authors to provide any missing information.

5.2 Methods of parasite detection

Given its ubiquity as a means for malaria diagnosis, the preferred parasite detection method was microscopy. No differentiation was made between light and fluorescent microscopy. The quality of slide reading [132,133], variations in sensitivity/specificity between RDTs [134], the ability of field teams to reliably read RDTs [135-138] or variations based on the selection of primers for PCR [139] all influence descriptions of prevalence and will have intrinsic variance between surveys included in the database. RDTs have been shown to yield higher false positive rates than microscopy [134,140,141] but seem to stratify both the lowest (<1% parasite rate) and highest (> 50% parasite rate) more accurately compared to routine microscopy [133,141]. An analysis of a large collection of community parasite rate data have shown that there was minimal difference in estimates of overall mean *P. falciparum* prevalence in matched paired analysis of community survey data that used microscopy and RDT for parasite examination [46]. Nevertheless, the differences between RDTs and microscopy in their ability to detect low grade infections when managed under routine conditions remains an inherent systematic bias in the data [141] that we are unable to control for; equally we are unable to control for the quality between survey investigations using only microscopy.

The largest problem of microscopy, when mounted as part of national sample surveys, has been the quality of slide preparation (staining and storage) and/or the guarantees of quality controlled

(QC) slide reading. Here we have had to make several value judgements in consultation with those responsible for the national surveys. For example national household surveys in Sudan, Somalia, Malawi and Angola we elected to include RDT data over slide read estimates of infection prevalence, whereas examples such as Kenya and Uganda we were assured of the QC expert slide reading from laboratory assistant aided blood sampling during malaria indicator surveys. There has been no hard and fast rules applied to these decisions, rather where evidence has been provided to use slides over RDTs we have done so.

5.3 Survey location geo-coding

Data geo-coding, defining a decimal longitude and latitude for each survey location, was a particularly demanding task. According to their spatial representation, data were classified as individual villages, communities or schools or a collection of communities within a definable area, corresponding to an area within a 5 km grid or approximately 0.05 decimal degrees at the equator. Where possible we aimed to retain disaggregated village, "point" level data rather than data across a "wide-area". Where data were reported across communities that exceeded at 5 km grid we regarded these as too low a spatial resolution, with significant possible variation within the polygon of information to be excluded when using advanced geo-statistical modeling. In practice this was a difficult criterion to audit as most survey reports did not provide enough detail on the size of the area surveyed.

More recent use of Global Positioning Systems (GPS) during survey work does enable a re-aggregation of household survey data with greater precision and useful in maintaining 5 km grid criteria while combining clusters of small sample sizes in space. The use of GPS to record longitudes and latitudes has been an important addition to national household sample surveys since *circa* 2007 [142]. However, in DHS household surveys managed by the ICF-MEASURE programme a GPS coordinate displacement process is carried out so that for urban clusters a displacement is introduced at a distance up to 2 km, which rarely effects the overall accuracy for modeling purposes as it is within the urban extent. For rural clusters a displacement is made up to 5 km, with a further, randomly-selected 1% of rural clusters displaced a distance up to 10 km. Here we have reviewed every rural cluster using Google Earth to examine the extent to which rural clusters might have been displaced to unpopulated areas and re-positioned to the nearest populated settlement.

To position each survey location where GPS coordinates were not available we used a variety of digital resources, amongst which the most useful were Microsoft Encarta Encyclopedia (Microsoft, 2004) and Google Earth (Google, 2009). Other sources of digital place name archives routinely used included GEOnet Names Server of the National Geospatial-Intelligence Agency, USA [143]; Falling Rain Genomics' Global Gazetteer [144]; Alexandria Digital Library prepared by University of California, USA [145]; African Data Sampler [146]; MapCarta [147]; Maplandia [148]; Global geodatabase-cities [149]; Open Street Map [150]; VMAP0 [151] and IslamicFinder [152].

Across Africa a number of national digital, GPS confirmed, place-name gazetteers exist for populated places, health facilities or schools. These are increasing in number, precision and

coverage. These were obtained on request from national census bureau's, ministries of education and health and NGO partners and proved to be valuable locating communities in Burkina Faso, Kenya, The Gambia, Mozambique, Madagascar, Somalia, Malawi, Mauritania, Ghana, Niger, Namibia, Senegal, Somalia, South Africa, Tanzania, Uganda, Zambia and Zanzibar.

Although standard nomenclatures and unique naming strategies are attempted in digital gazetteers [153], these are difficult to achieve at national levels where spellings change between authors, overtime and where the same place names are replicated across a country. As such, during the data extraction, each data point was recorded with as much geographic information from the source as possible and this was used during the geo-positioning, for example checking the geo-coding placed the survey location in the administrative units described in the report or corresponded to other details in the report on distance to rivers or towns when displayed on Google Earth. While in theory GPS coordinates should represent an unambiguous spatial location, these required careful re-checking to ensure that the survey location matched the GPS coordinates. As routine we therefore rechecked all GPS data from all sources using place names and/or Google Earth to ensure coordinates were located on communities.

All coordinates were subject to a final check using second level administrative boundary Global Administrative Units Layers (GAUL) spatial database developed and revised in 2008 by Food and Agriculture Organization (FAO) of the United Nations [154]. The spatial selection tool in ArcGIS 10.1 (ESRI, USA) was used to verify points whether along the coastline were located on land as defined by GAUL 2008. The Global lakes and Wetlands (GLWD) database developed by the World Wildlife Fund [155] was used to ensure inland points were positioned on land and not waterbodies. Here we aimed to identify survey coordinates that fell slightly off the coastline, located on the river or in incorrect administrative units, every anomaly was re-checked and re-positioned using small shifts in combination with Google Earth.

5.4 Defining national boundaries

At the end of World War II in 1945, nearly every country in Africa was subject to colonial rule or administration. Every country on mainland Africa is now independent, while a few islands remain under European administration (Reunion and Mayotte). There are currently 55 independent States, 53 are members of the African Union. Throughout this report we use the current names and boundaries of nation states in Africa, rather than pre-independence nomenclature and boundaries. Throughout we have used as a basis for delineating national boundaries provided under UN sponsored boundary digital processing [156]. As such we treat South Sudan separate from The Republic of Sudan and Eritrea separate from Ethiopia. There are many disputed areas of Africa, claimed by neighboring countries and remain unresolved [157]. For the purposes of our work we have treated the Ilemi Triangle as part of Kenya's Turkana region. We have regarded Walvis Bay in Namibia as always being part of Namibia, despite being a territory of South Africa for many years since Namibia's independence in 1990. Two small territories within the Kingdom of Morocco continue to be occupied by Spain in the North West (Ceuta) and North-East (Melilla) on the Mediterranean coastline, however, we considered part of the Kingdom approximating to its Ottoman extent before 1912. We treat the Sinai Peninsula as permanently part of The United

Arab Republic of Egypt. Without making any political judgments we regard the region Abeyi as part of the Republic of Sudan, however, in national mapped products both countries include this region. The Hala'ib Triangle on the Sudan-Egyptian border we treat as part of Sudan, although that since 2010 Egypt controls this area as part of its Red Sea State. The Bakassi region, a disputed border territory on the Atlantic coast between Nigeria and Cameroon we treat as part of Nigeria, despite final implementation of agreements for Cameroonian administration in 2014. The island groups of Bioko/Annobin and Zanzibar are treated separately from mainland Equatorial Guinea and Tanzania respectively. These island groups have historically had different malaria control plans and elimination ambitions to their mainland counterparts.

5.5 Age standardization

Where age was not specified in the report for each survey but stated that the entire village or primary school children examined we assumed age ranges to be 0-99 years or 5-14 years respectively. There was a large diversity in the age ranges of sampled populations between studies. To make any meaningful comparisons in time and space a single standardized age range is required. Correction to a standard age for *Plasmodium falciparum* is possible based on the observation and theory of infectious diseases where immunity is acquired following repeated exposure from birth. We have adapted catalytic conversion Muench models, first used in malaria by Pull & Grab in the 1970s [158], into static equations in R-script that uses the lower and upper range of the sample and the overall prevalence to transform into a predicted estimate in children aged 2-10 years, *Pf*$PR_{2\text{-}10}$ [96].

5.6 Sample size restrictions

Sample size is inversely related to prevalence where, at low sample sizes, biases in prevalence estimates are introduced, dependent on the true prevalence of the population and translates into large standard errors [159]. There is a critical threshold of between 10 and 20 individuals sampled, below which the standard error increases exponentially in most surveys of parasitic infections and the curve starts to flatten at a sample size of about 50 and reaches an asymptote at about 100 [160]. The sample size of individual survey samples is also important in the derivation of correlations with covariates of endemicity, in testing plausible associations between say rainfall and prevalence during covariate selection small, imprecise samples can lead to over-fitting. We aimed to combine communities in close proximity where any village had less than 10 people sampled and where communities were within 5 km of each other, sampled at exactly the same time by the same investigators.

6. Data sharing, data access

The data assembled for this study are part of a wider initiative to support national governments with evidence platforms to design malaria control, the INFORM project [131,161] supported by the Department for International Development, UK and The Wellcome Trust. The geo-coded parasite prevalence data from published, archived and unpublished data assembled into carefully curated databases must be owned and subsequently managed by malaria control departments

within national ministries of health. National research and ministry of health survey data are the property of national governments. More often than not most ministries of health do not have access to the full range of malaria data potentially available within their own country. The aim therefore is to use the INFORM project to build an ownership of national malaria data and make available all assembled data to Ministries of Health across Africa and the regional technical advisors of the World Health organization. As such national governments will become the custodians of their own national data and have full responsibility for its distribution to national, regional and international scientists and control partners.

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