PLOS GLOBAL PUBLIC HEALTH

RESEARCH ARTICLE

# Global estimates of pregnancies at risk of *Plasmodium falciparum* and *Plasmodium vivax* infection in 2020 and changes in risk patterns since 2000

**Georgia R. Gore-Langton[1]*, Jorge Cano[1,2], Hope Simpson[1], Andrew Tatem[3], Natalia Tejedor-Garavito[3], Adelle Wigley[3], Alessandra Carioli[3], Peter Gething[4,5], Daniel J. Weiss[4,5], Daniel Chandramohan[1], Patrick G. T. Walker[6], Matthew E. Cairns[7], R. Matthew Chico[1]**

**1** Department of Disease Control, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom, **2** Expanded Special Project for Elimination of Neglected Tropical Diseases, WHO Regional Office for Africa, Brazzaville, Democratic Republic of the Congo, **3** WorldPop, Geography and Environmental Science, University of Southampton, Southampton, United Kingdom, **4** Malaria Atlas Project, Telethon Kids Institute, Perth Children's Hospital, Nedlands, Australia, **5** Faculty of Health Sciences, Curtin University, Bentley, Australia, **6** Faculty of Medicine, School of Public Health, Imperial College London, London, United Kingdom, **7** Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom

* georgia.gore-langton@lshtm.ac.uk

Check for updates

OPEN ACCESS

**Citation:** Gore-Langton GR, Cano J, Simpson H, Tatem A, Tejedor-Garavito N, Wigley A, et al. (2022) Global estimates of pregnancies at risk of *Plasmodium falciparum* and *Plasmodium vivax* infection in 2020 and changes in risk patterns since 2000. PLOS Glob Public Health 2(11): e0001061. https://doi.org/10.1371/journal.pgph.0001061

**Editor:** Mathieu Nacher, Centre hospitalier de Cayenne, FRANCE

**Received:** April 12, 2022

**Accepted:** October 3, 2022

**Published:** November 9, 2022

**Copyright:** © 2022 Gore-Langton et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** All data are publicly available from WorldPop https://www.worldpop.org/ and Malaria Atlas Project https://malariaatlas.org/. All analyses were implemented in R version 4.0.3 and all code was reviewed by two authors.

**Funding:** WorldPop work was funded in part by the Wellcome Trust (grant number: 204613/Z/16/Z), the UK Foreign, Commonwealth and Development Office, and, by the Bill and Melinda Gates Foundation (grant number INV-007594). Matt

## Abstract

### Background

Women are at risk of severe adverse pregnancy outcomes attributable to *Plasmodium spp*. infection in malaria-endemic areas. Malaria control efforts since 2000 have aimed to reduce this burden of disease.

### Methods

We used data from the Malaria Atlas Project and WorldPop to calculate global pregnancies at-risk of *Plasmodium spp*. infection. We categorised pregnancies as occurring in areas of stable and unstable *P. falciparum* and *P. vivax* transmission. We further stratified stable endemicity as hypo-endemic, meso-endemic, hyper-endemic, or holo-endemic, and estimated pregnancies at risk in 2000, 2005, 2010, 2015, 2017, and 2020.

### Findings

In 2020, globally 120.4M pregnancies were at risk of *P. falciparum*, two-thirds (81.0M, 67.3%) were in areas of stable transmission; 85 2M pregnancies were at risk of *P. vivax*, 93.9% (80.0M) were in areas of stable transmission. An estimated 64.6M pregnancies were in areas with both *P. falciparum* and *P. vivax* transmission. The number of pregnancies at risk of each of *P. falciparum* and *P. vivax* worldwide decreased between 2000 and 2020, with the exception of sub-Saharan Africa, where the total number of pregnancies at risk of *P. falciparum* increased from 37 3M in 2000 to 52 4M in 2020.

Cairns: Matthew E Cairns is supported by a Sir Henry Dale Fellowship jointly funded by the 15 Wellcome Trust and the Royal Society (Grant Number 220658/Z/20/Z). Georgia R Gore-Langton is supported by an MRC PhD studentship (MR/N013638/1). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** The authors have declared that no competing interests exist.

## Interpretation

Historic investments in malaria control have reduced the number of women at risk of malaria in pregnancy in all endemic regions except sub-Saharan Africa. Population growth in Africa has outpaced reductions in malaria prevalence. Interventions that reduce the risk of malaria in pregnancy are needed as much today as ever.

## Introduction

### Plasmodium falciparum

*Plasmodium falciparum* infection during pregnancy increases the risk of spontaneous abortion [1], stillbirth [1], preterm delivery [2], low birthweight [3], small for gestational age [4], maternal and newborn anaemia [5], and maternal death [2, 4, 6]. In areas of high *P. falciparum* transmission, pregnant women develop partial immunity to placental infection through repeated malaria exposure over successive pregnancies [7–10]. The adverse effects of *P.falciparum* are largely due to the sequestration of the parasite within the placenta and are particularly seen in women who have not been exposed to *P. falciparum* in any previous pregnancy. The density and frequency of infection and the risk of associated adverse pregnancy outcomes are greatest among primigravidae, decreasing with each subsequent pregnancy.

The vast majority of global *P. falciparum* cases are in sub-Saharan African, whereas lower transmission persists across parts of South America and Asia [11, 12]. To protect pregnant women against the adverse consequences of malaria infection where transmission is moderate to high, the World Health Organization (WHO) recommends antenatal use of long-lasting insecticide-treated nets, active case management during pregnancy, and the provision of intermittent preventative treatment (IPTp) with sulfadoxine-pyrimethamine (SP) during scheduled antenatal care (ANC) visits from the second trimester to delivery [13]. Where *P. falciparum* transmission is low or unstable, there are no specific WHO prevention recommendations.

### Plasmodium vivax

*Plasmodium vivax* is also associated with stillbirth [1], preterm delivery [14], low birthweight [15, 16], and anaemia [16–18], but infection during pregnancy is considered less severe than *P. falciparum* in part because *P. vivax* infects only reticulocytes which limits parasite densities [18]. However, prevention and management of *P. vivax* infection can be challenging due to recrudescent and relapsing infections. Primaquine is used to treat *P.* vivax and is capable of eliminating liver-stage hypnozoites, but is contraindicated in pregnancy because of the potential to induce haemolysis and blood disorders in the fetus. Radical cure in pregnancy is not recommended until after delivery [13, 18]. Moreover, all gravidae infected with *P. vivax* are equally vulnerable to having low birthweight newborns [18]. Most *P. vivax* cases are in geographic areas of the WHO Regional Offices for South-East Asia and Eastern Mediterranean [19] where there are currently no WHO recommendations specifically for preventing these infections in pregnancy.

Global estimates of pregnancies at risk of malaria have not been generated since 2007 [20]. The most recent regional estimates were for 2020 and were specific to *P. falciparum* in sub-Saharan Africa [11]. Since 2007 there have been decreases in the prevalence of *P. falciparum* [12] and *P. vivax* [19], as well as global fertility rates [21, 22], although absolute populations have grown at regional and global levels. To support the data needs of policymakers and

programme managers who are responsible for ongoing malaria control and elimination efforts in their advocacy for resources for malaria in pregnancy interventions and research, we have generated contemporary estimates of pregnancies at risk of *P. falciparum* and *P. vivax* stratified by transmission intensity.

## Methods

### Malaria estimates

The rate of *P. falciparum* infection among 2 to 10 year olds, as generated by the Malaria Atlas Project (MAP), has been used as a proxy for malaria among pregnant women [23, 24]. We obtained global estimates of mean *P. falciparum* and *P. vivax* parasite rates (all ages) from MAP as raster datasets at $5km^2$ resolution. These estimates incorporate prevalence data from household surveys, case data, and socio-economic and environmental data to produce smoothed, global estimates of malaria parasite rate (hereafter referred to as prevalence) [12, 25]. For our 2020 estimated pregnancies at risk of malaria infection, we calculated the central, lower, and upper (mean, 2 $5^{th}$ and 97 $5^{th}$ percentile, respectively) prevalence estimate for every $5km^2$ globally from 100 realisations of the underlying joint posterior prevalence of *P. falciparum* and *P. vivax*. For years 2000, 2005, 2010, 2015, and 2017 we used mean prevalence estimates as generated by MAP.

### Pregnancy estimates

We obtained global estimates of total pregnancies at $1km^2$ resolution from WorldPop. These data are based on age and sex structures of global population at $1km^2$ to estimate the number of children under one year of age. An extrapolation factor is then applied to correct for child mortality and to estimate the number of livebirths, which is then standardised to the United Nations total national number of livebirths [26–28]. Country specific numbers of stillbirths, miscarriages, and abortions are incorporated to estimate the ratio of livebirths to pregnancies [29]. yielding numbers of pregnancies per $1km^2$ for all African, Asian, and Latin American and Caribbean countries.

### Pregnancies at risk of malaria

We aggregated pregnancy estimates to the same resolution as MAP estimates ($5km^2$) for all malaria-endemic countries and matched these to the corresponding year of malaria prevalence. Pregnancy-weighted malaria prevalence was averaged at the smallest administrative level of each country. For 2020, we classified pregnancies as being at risk of stable ($\geq$0 01%, i.e. $\geq$ one case among 10,000 people per annum) or unstable (>0% and <0 01%) transmission based on the central, lower, and upper estimates of malaria prevalence [20]. We quantified overall pregnancies at risk by regions of the Sustainable Development Goals (SDG) and country, and by stable or unstable transmission, rounding the number of pregnancies at risk to the nearest hundred. We considered pregnant women resident in areas with both *P. falciparum* and *P. vivax*, stable or unstable, at risk of mixed infections. We further categorised stable malaria endemicity as hypo-endemic (0 01 to 10% inclusive), meso-endemic (11 to 50% inclusive), hyper-endemic (51 to 75 inclusive %) and holo-endemic (>75%) and summed pregnancy estimates by categorical endemicity for years 2000, 2005, 2010, 2015, 2017, and 2020 [30]. Finally, to investigate the impact of malaria control efforts over the past two decades, we calculated the hypothetical number of pregnancies at risk of each level of *P. falciparum* endemicity using WorldPop pregnancy estimates for 2020 and MAP prevalence estimates for

2000 and assumed that the number of pregnancies in 2020 no longer at risk of infection, or at lower risk of infection, were attributable to antimalarial interventions since 2000.

### Structure of results section

We first present 2020 global results for *P. falciparum* followed by *P. vivax*. We then report the proportion of at risk pregnancies by *P. falciparum* prevalence for all countries in sub-Saharan Africa and for *P. vivax* for countries where more than 10% of at risk pregnancies are in areas of stable transmission. We subsequently present pregnancies at risk of unstable/hypo-/meso-/hyper-/holo-endemic malaria for 2000, 2005, 2010, 2015, 2017, 2020 by malaria species. Finally, we report the change in the number of pregnancies at risk of *P. falciparum* in 2020 compared to the counterfactual number of pregnancies that would have been at risk had malaria prevalence remained at 2000 levels.

### Role of the funding source

The study sponsors had no role in any stage of data analysis or manuscript development.

## Results

### *Plasmodium falciparum*: Stable versus unstable transmission

In 2020, 120 4M pregnancies were at risk of *P. falciparum* transmission worldwide (Table 1). Over half of these (81.0M, 67.25%) were in areas of stable (≥0 01%) transmission. The majority of global pregnancies at risk of stable transmission were in sub-Saharan Africa, 52 4M (Table 1). Considering SDG regions, Central and Southern Asia had the second largest number of pregnancies at risk of stable *P. falciparum*, 19.4M, making up 40 53% of total pregnancies at risk in the region, the remaining pregnancies were at risk of unstable *P. falciparum* (Table 1). The provision of IPTp is WHO policy in all areas of meso-endemic (11 to 50%) or higher transmission within sub-Saharan Africa [31]. An estimated 34 8M pregnancies met these criteria in 2020 (S1 Table), with a further 93,100 pregnancies exposed to similar levels of transmission outside of sub-Saharan Africa.

In 2020, 39.4M pregnancies globally were at risk of unstable *P. falciparum* transmission (Table 1).

With the exceptions of sub-Saharan Africa and Northern Africa and Western Asia, the majority of at risk pregnancies across SDG regions were in areas of unstable *P. falciparum* transmission. Central and Southern Asia had the largest number of pregnancies at risk of unstable *P. falciparum* (28 5M) making up 59.47% of the region's at risk pregnancies. Eastern and South-Eastern Asia had the second highest number of pregnancies at risk of unstable *P. falciparum* transmission, 6.1M, accounting for 60 7% of at risk pregnancies in the region (Table 1).

## Countries and regions of sub-Saharan Africa

### Population at risk

In East Africa, Ethiopia had the most pregnancies at risk of *P. falciparum*, 5 2M, of which 99 7% were in areas of stable transmission (Fig 1), although prevalence was relatively low (mean 2 3% IQR: 0 1 to 5 6) (S2 Table). In West Africa, Nigeria had the most pregnancies at risk, 10 7M, all of which were in areas of stable *P. falciparum* transmission where the mean prevalence was 29 9% (IQR: 15 8 to 43 7). In Central Africa, the Democratic Republic of Congo (DRC) had the most pregnancies at risk of *P. falciparum* infection, 5 3M, all in areas of stable transmission where the mean prevalence was 39 7% (IQR: 8 9 to 68 8) (Fig 1 and S2 Table).

**Table 1. Pregnancies at risk of *Plasmodium falciparum* and *Plasmodium vivax* in 2020 by regions of the Sustainable Development Goals disaggregated by stable and unstable transmission.**

| | *Plasmodium falciparum* | | | | |
|---|---|---|---|---|---|
| | | Stable transmission (> = 0.01%) | | Unstable transmission (<0.01%) | |
| SDG region | Total pregnancies at risk | Pregnancies at risk ($2.5^{th}$ to $97.5^{th}$ percentile) | % of total pregnancies ($2.5^{th}$ to $97.5^{th}$ percentile) | Pregnancies at risk ($2.5^{th}$ to $97.5^{th}$ percentile) | % of total pregnancies ($2.5^{th}$ to $97.5^{th}$ percentile) |
| Northern Africa & Western Asia | 4,131,700 | 3,243,300 (2,714,300–3,259,500) | 78.50 (65.69–78.89) | 888,400 (872,200–1,417,400) | 21.50 (21.11–34.31) |
| Sub-Saharan Africa | 52,395,400 | 52,320,300 (52,132,600–52,352,900) | 99.86 (99.50–99.92) | 75,100 (42,600–262,800) | 0.14 (0.08–0.50) |
| Central & Southern Asia | 47,849,200 | 19,393,500 (4,805,600–32,302,300) | 40.53 (10.04–67.51) | 28,455,700 (15,546,900–42,030,500) | 59.47 (32.49–87.84) |
| Eastern & South-Eastern Asia | 10,090,300 | 3,968,300 (211,500–6,029,700) | 39.33 (2.10–59.76) | 6,122,000 (4,060,600–9,878,800) | 60.67 (40.24–97.90) |
| Latin America & the Caribbean | 5,979,000 | 2,075,700 (89,000–2,620,200) | 34.72 (1.49–43.82) | 3,903,300 (3,176,600–5,453,100) | 65.28 (53.13–91.20) |
| Global Total | 120,445,600 | 81,001,100 (59,953,000–96,564,600) | 67.25 (49.78–80.17) | 39,444,500 (23,698,900–59,042,600) | 32.75 (19.68–49.02) |
| | *Plasmodium vivax* | | | | |
| | | Stable transmission (> = 0.01%) | | Unstable transmission (<0.01%) | |
| | Total pregnancies at risk | Pregnancies at risk ($2.5^{th}$ to $97.5^{th}$ percentile) | % of total pregnancies ($2.5^{th}$ to $97.5^{th}$ percentile) | Pregnancies at risk ($2.5^{th}$ to $97.5^{th}$ percentile) | % of total pregnancies ($2.5^{th}$ to $97.5^{th}$ percentile) |
| Northern Africa & Western Asia | 3,077,900 | 2,776,300 (2,712,200–2,822,800) | 90.20 (88.12–91.71) | 301,600 (255,100–365,700) | 9.80 (8.29–11.88) |
| Sub-Saharan Africa | 6,995,700 | 6,985,300 (6,985,300–6,985,300) | 99.85 (99.85–99.85) | 10,400 (10,400–10,400) | 0.15 (0.15–0.15) |
| Central & Southern Asia | 54,564,600 | 51,748,000 (51,175,600–52,601,500) | 94.84 (93.79–96.40) | 2,816,600 (1,963,100–3,389,000) | 5.16 (3.60–6.21) |
| Eastern & South-Eastern Asia | 12,900,200 | 12,279,300 (9,995,100–12,490,600) | 95.19 (77.48–96.82) | 620,900 (409,600–2,905,100) | 4.81 (3.18–22.52) |
| Latin America & the Caribbean | 7,649,400 | 6,182,900 (4,386,000–6,539,600) | 80.83 (57.34–85.49) | 1,466,500 (1,109,800–3,263,400) | 19.17 (14.51–42.66) |
| Global Total | 85,187,800 | 79,971,800 (75,254,200–81,439,800) | 93.88 (88.34–95.60) | 5,216,000 (3,748,000–9,933,600) | 6.12 (4.40–11.66) |

https://doi.org/10.1371/journal.pgph.0001061.t001

## Prevalence of at risk population

Liberia was the country with the highest mean prevalence of *P. falciparum* within sub-Saharan Africa, 49 3% (IQR: 31 8 to 62 9) in areas of stable transmission and 214,600 pregnancies at risk, followed by DRC, as described above, and Sierra Leone, mean prevalence 39 2% (IQR: 22 7 to 46.0) and 328,800 pregnancies at risk. The top five countries globally with most pregnancies at risk of stable *P. falciparum* transmission were, in descending order: India, Nigeria, DRC, Ethiopia, and Pakistan; mean prevalence was highest in DRC and Nigeria. The top five countries with the most pregnancies in areas of unstable *P. falciparum* transmission (<0 01% prevalence) were, in descending order: India, Indonesia, Brazil, Afghanistan, and Vietnam.

## High burden high impact countries

Eleven countries are considered "High burden to high impact countries" that account for approximately 70% of the global *P. falciparum* [32]. Among these, India had the most

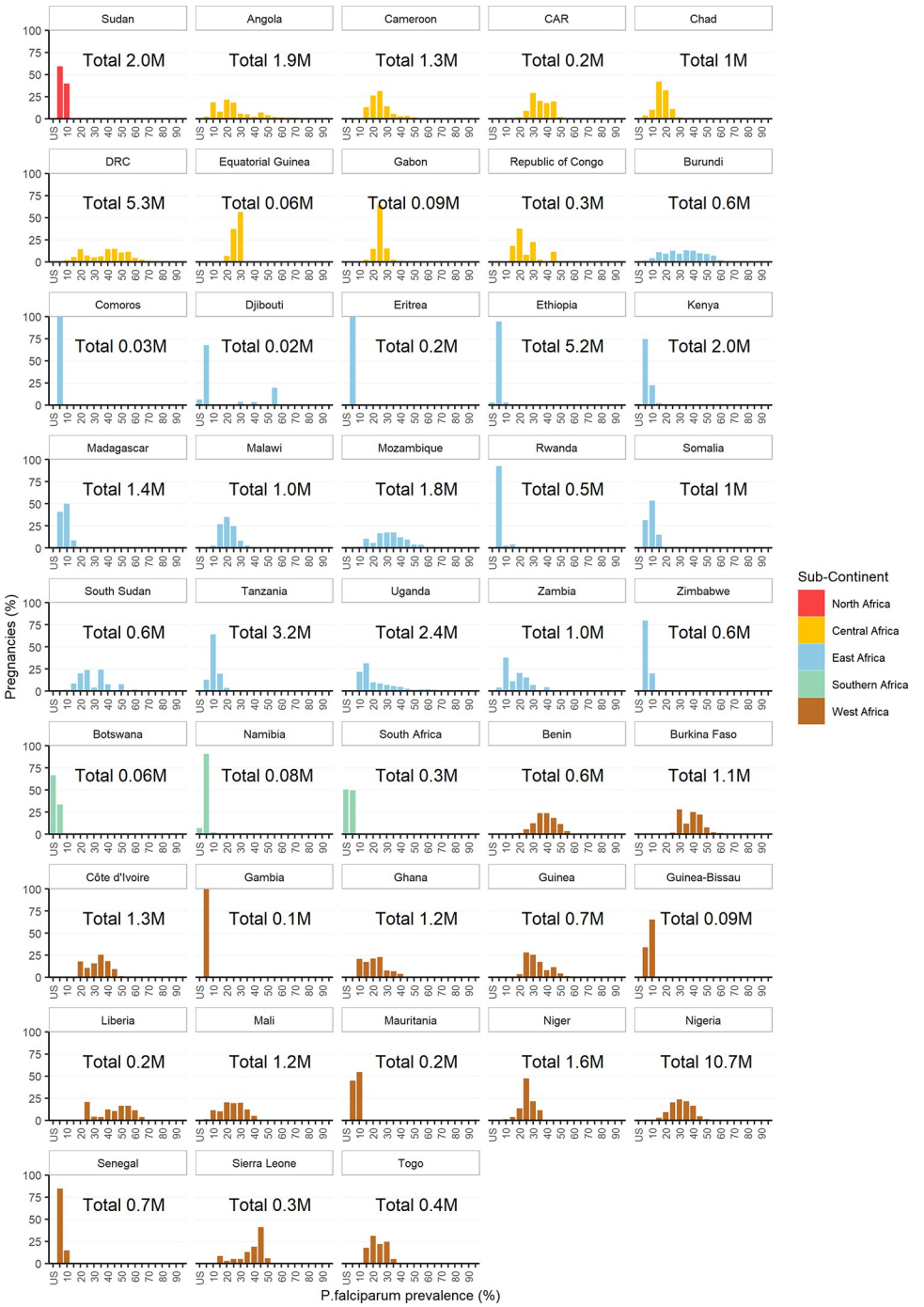


**Fig 1. Proportion and total number of pregnancies at risk of *Plasmodium falciparum* in Africa in 2020 by country and prevalence (%); US = unstable (0> and <0 01%).**

https://doi.org/10.1371/journal.pgph.0001061.g001

pregnancies at risk of *P. falciparum* (37 5M), of which 38.0% were at risk of stable but low transmission (mean: 0 23%; IQR: 0 01 to 1.61) (S1 Fig and S2 Table). Among this group of countries Nigeria and DRC had the next highest numbers of pregnancies at risk as detailed above (S1 and S2 Figs).

### *Plasmodium vivax*

Worldwide, 85 2M pregnancies were at risk of *P. vivax*, of which 80 0M (93 9%) were in areas of stable transmission. The majority of pregnancies at risk of stable *P. vivax* transmission were in Central and Southern Asia (51 7M), accounting for 94 8% of all pregnancies at risk of *P. vivax* in the region. Globally, 5.2M pregnancies were in areas of unstable *P. vivax* transmission. A total of 7 0M pregnancies within sub-Saharan Africa were at risk of *P. vivax* (99.9% of which in areas of stable transmission).

The proportion of pregnancies at risk of stable *P. vivax* by prevalence is shown in Fig 2 for countries where more than 10% of the pregnancies at risk of *P. vivax* were in areas of stable transmission. India had the largest number of pregnancies at risk of *P.vivax*, 38 3M, 97.2% of these (37.2M) were in areas of stable transmission where mean prevalence was 0 4%, IQR: 0 06 to 0 97, followed by Pakistan with 10.3M pregnancies all at risk of stable transmission, mean prevalence 0.76, IQR: 0.07 to 1.65). Indonesia had the third largest number of pregnancies at risk of *P.vivax*; in total 6.7M pregnancies were at risk, 96.8% (6.5M) of these were in areas of stable transmission where mean prevalence was 0.55, IQR: 0.03 to 2.24).

## Mixed infections

Worldwide, 64.6M pregnancies in 2020 were resident in areas of both *P. falciparum* and *P. vivax* transmission, and therefore at risk of mixed infections. The majority of these (41 5M, 64 2%) were within Central & Southern Asia (S3 Table and S3 Fig).

## Changes from 2000 to 2020

The total number of pregnancies at risk of *P. falciparum* or *P. vivax* globally decreased between 2000 and 2020 (Fig 3A and Fig 3B). Despite malaria prevalence having decreased overall in sub-Saharan Africa since 2000, and the number and proportion of pregnancies exposed to hyper- (51 to75%) or holo-endemic (>75%) malaria decreasing, the total number of pregnancies at risk of *P. falciparum* increased year-on-year between 2000 and 2020 in sub-Saharan Africa from 37 3M to 52 4M (Fig 3C and S4 Table), with nearly all of these pregnancies in areas of stable transmission. This rise was driven by an increase in the number of pregnancies at risk of lower levels of transmission (hypo- [0.01 to 10%] and meso-endemic [11 to 50%]) (Fig 3C and S4 Fig). There were 10.4M fewer pregnancies in areas of hyper- (51 to 75%) or holo-endemic (>75%) *P. falciparum* in 2020 than in 2000, and 25.7M more pregnancies in areas of the lower levels of hypo-endemic (0.1 to 10%) or meso-endemic (11 to 50%) *P. falciparum* in 2020 than in 2000 (S4 Fig). The number of pregnancies residing in areas of meso-endemic (11 to 50%) transmission or higher within sub-Saharan Africa, and therefore eligible for IPTp, increased from 30 0M in 2000 to 34 8M in 2020, with the steepest rise between 2017 and 2020 (Fig 4 and S1 Table). The number and percentage of pregnancies by *P. falciparum* endemicity is shown by year for African countries in S5 and S6 Figs.

Across Asia, pregnancies at risk of *P. falciparum* decreased from 2000 to 2020, as did the proportion of at risk pregnancies in areas of higher transmission levels (Fig 3C). Global pregnancies at risk of *P. vivax* decreased between 2000 and 2020, with a slight increase between 2017 and 2020. The number and proportion of pregnancies by *P. vivax* endemicity is shown by year for Asian countries in S7 and S8 Figs. In sub-Saharan Africa, numbers at risk of *P. vivax* increased from 5.9M in 2000 to 7.0M in 2020 (Fig 3D).

The total number of pregnancies (including those not at risk of malaria) in countries with endemic *P. falciparum* has increased between 2000 and 2020 while the proportion of pregnancies at risk of *P. falciparum* (stable or unstable) has decreased; 75.5% of all pregnancies in *P. falciparum* endemic countries in 2000 were in areas of malaria transmission, reducing to

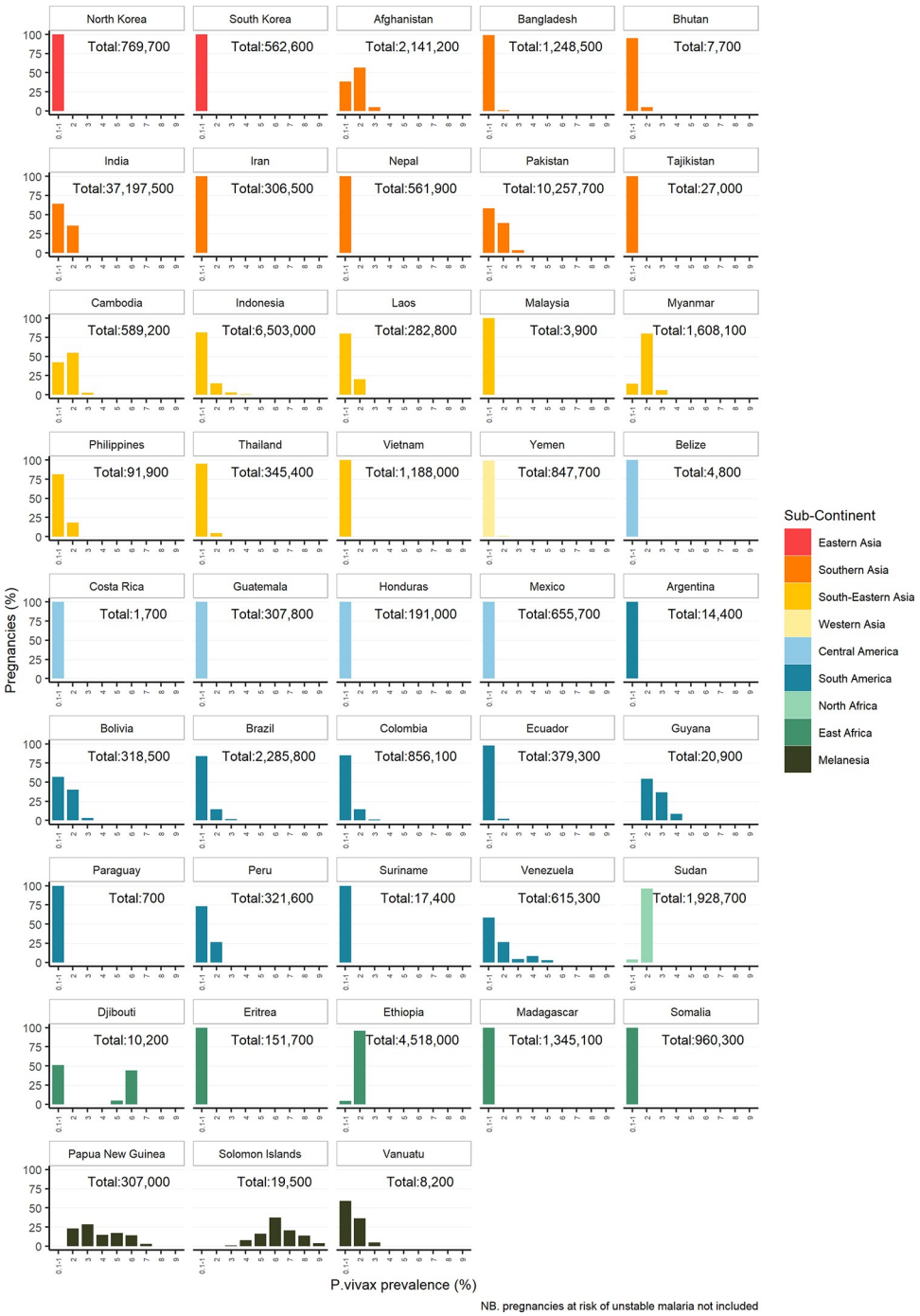


**Fig 2. Proportion and total number of pregnancies at risk of stable *Plasmodium vivax* in 2020 in countries where >10% of total at-risk pregnancies are at-risk of stable transmission.**

https://doi.org/10.1371/journal.pgph.0001061.g002

62.8% in 2020 (S9 Fig and S4 Table). The total number of pregnancies in countries endemic for *P. vivax* has decreased between 2000 and 2020, as did the proportion of total pregnancies at risk of *P. vivax;* 95.6% of all pregnancies within countries with endemic *P. vivax* were at risk of *P. vivax* in 2000, reducing to 59.5% in 2020. In sub-Saharan Africa, there has been a

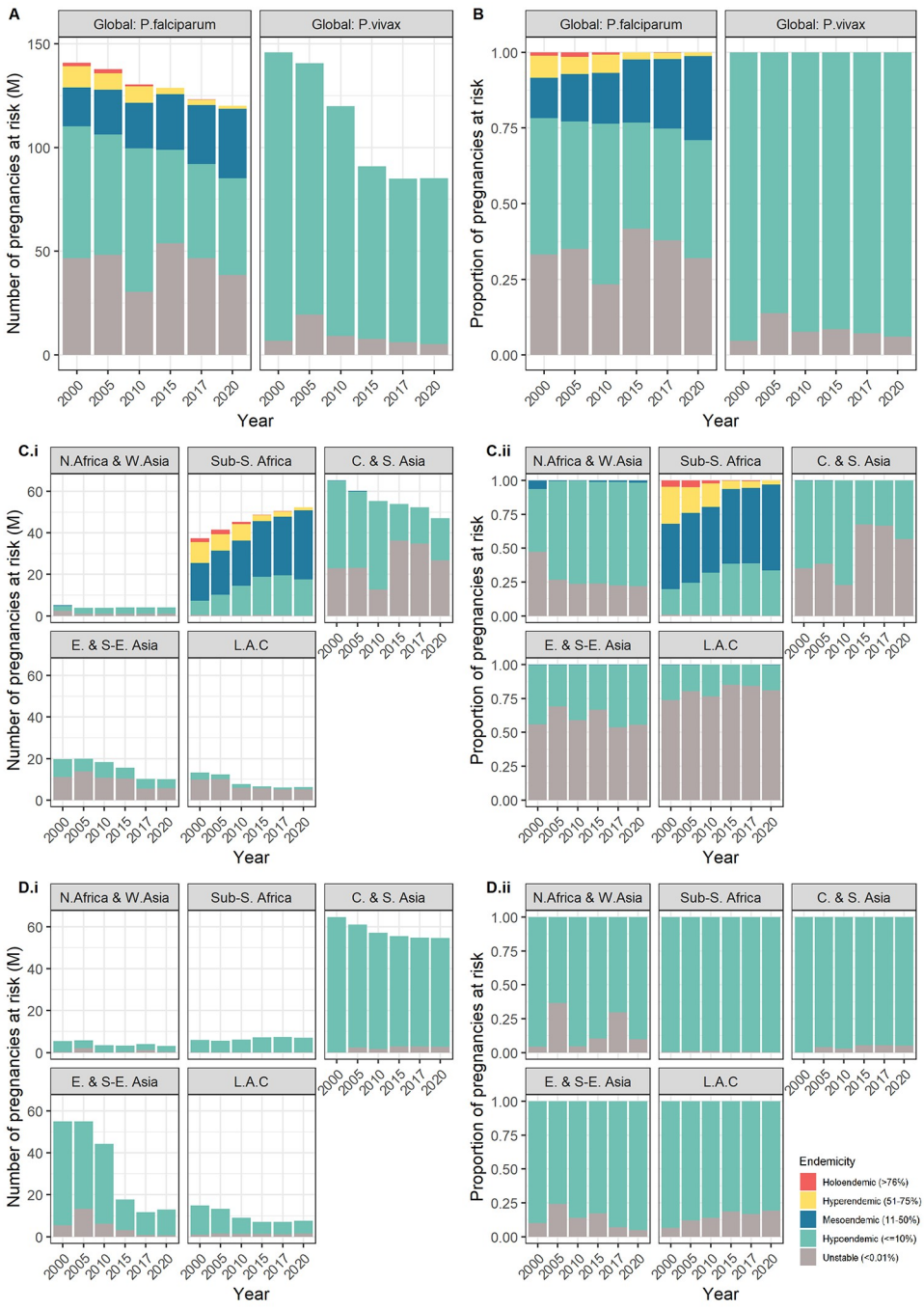


**Fig 3.** Number (A) and proportion (B) of pregnancies at risk of *Plasmodium falciparum* and *Plasmodium vivax* globally from 2000 to 2020, and number (C.i) and proportion (C.ii) of pregnancies at risk of *Plasmodium falciparum* and *Plasmodium vivax* (D.i and D.ii) from 2000 to 2020 by SDG region.

https://doi.org/10.1371/journal.pgph.0001061.g003

year-on-year increase in both the total number of pregnancies and the proportion of total pregnancies at risk of each of *P. falciparum* and *P. vivax*, applicable to the six African countries for which MAP generate *P. vivax* transmission (Ethiopia, Eritrea, Djibouti, Somalia, Sudan, and Madagascar) (S9 Fig and S4 Table).

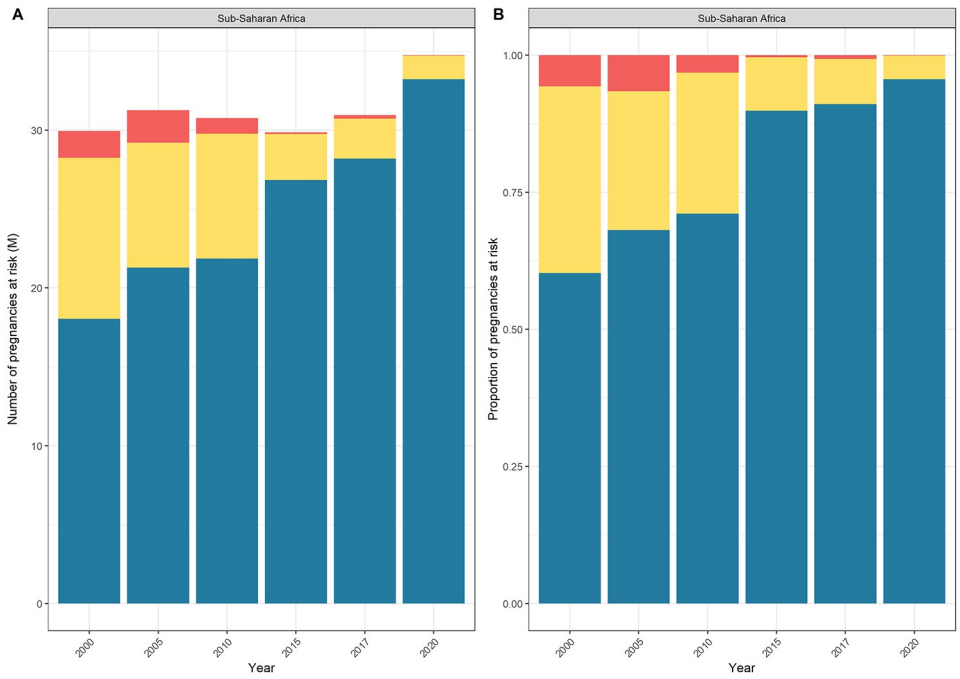


**Fig 4.** Number (A) and proportion (B) of pregnancies at risk of meso-endemic or higher (≥ 11%) *Plasmodium falciparum* transmission in sub-Saharan Africa, 2000 to 2020.

https://doi.org/10.1371/journal.pgph.0001061.g004

## Counterfactuals

In sub-Saharan Africa there were just over 2.4 million fewer pregnancies in 2020 in areas of holo-endemic (>75%) *P. falciparum* transmission and 13 4M fewer pregnancies in areas of hyper-endemic (51 to 75%) transmission than there would have been had prevalence remained at 2000 levels but pregnancies continued to increase to 2020 levels (S10 Fig). Thus, more pregnant women were resident in areas where transmission is less intense. Specifically, 16 1M more sub-Saharan pregnant women were living in hypo-endemic (0.1 to 10%) and meso-endemic (11 to 50%) areas in 2020 compared to 2000. In Central and Southern Asia, there were 13.5M pregnancies in 2020 in areas of no *P. falciparum* transmission which would have been at risk in 2000, and 5.1M more pregnancies in areas of unstable transmission (>0 and <0.01%), reflecting the reduction of 18 6M pregnancies in areas of hypo-endemic (0.1 to 10%) and meso-endemic (11 to 50%) transmission (S9 Fig).

## Discussion

We present contemporary global estimates of pregnancies at risk of *P. falciparum* and *P. vivax* and examine changes in risk by categorical endemicity since 2000. Despite decreases in *P. falciparum* and *P. vivax* prevalence, and decreases in the global number of pregnancies at risk of malaria, the number of pregnancies at risk of moderate to high *P. falciparum* transmission in sub-Saharan Africa i.e. women requiring preventative intervention, has remained relatively unchanged, increasing between 2017 and 2020. The scale up of antimalarial interventions for pregnant women throughout the antenatal period is needed today as much as ever and, indeed, should precede conception given that an estimated 70% of infections among primigravidae are acquired before pregnancy [9]. Redoubled efforts are needed to reduce malaria exposure with long-lasting insecticide nets and prompt case management among women of child bearing age.

Our analysis illustrates the challenges of reducing the number and proportion of pregnant women at risk of malaria infection in sub-Saharan Africa, where fertility rates are decreasing, but remain high (S10 Fig), and population growth is forecasted up to and after 2100 [33, 34]. While not an antimalarial intervention, efforts that strengthen family planning services in malaria-endemic countries contribute to maternal and child health as well as reduce the number of pregnancies at risk of malaria.

We have shown that malaria control efforts have led to a reduction in the number of pregnancies at risk of higher levels of *P. falciparum* transmission within sub-Saharan Africa, and a corresponding increase in the numbers at risk of lower levels of transmission. Across other regions, pregnancies at risk of hypo-endemic (>0.01 to 10%) transmission have decreased while the numbers in areas of unstable (<0.01%) or no *P. falciparum* transmission have increased. Approximately a third of all pregnancies at risk of *P. falciparum* worldwide were in areas of very low, unstable transmission where prevention recommendation are missing, and if they were to be present, would be operationally challenging to deploy and may be difficult to justify on a cost-effectiveness basis unless the value of malaria elimination is also taken into consideration. Nonetheless, this burden of disease is not insignificant given the very large number of pregnancies in consideration, the lower acquired levels of immunity in these transmission settings and the higher likelihood of infections evolving to clinical disease [35]. While pregnancies at risk of *P. vivax* are fewer in number and *P. vivax* commonly considered to be more benign than *P. falciparum*, research investment is urgently needed given the millions of pregnant women at risk of *P. vivax* infection for which there is no radical cure during pregnancy and increasingly strong evidence of its distribution across malaria-endemic Africa [36].

Women of all gravidities who reside in areas of unstable transmission are at risk of developing high-density placental infections with potential for adverse maternal and newborn health outcomes. The association between *P. falciparum* during pregnancy and stillbirth is stronger in areas of low to intermediate transmission than in areas of high transmission [1]. Access to rapid diagnosis and treatment of these uncommon but dangerous infections in areas of unstable transmission is important.

Within areas of stable transmission, malaria prevalence varied widely. The WHO recommends the provision of IPTp with sulfadoxine-pyrimethamine to pregnant women resident in areas of moderate to high *P. falciparum* transmission in Africa, an intervention that has potent anti-malarial and non-malarial effects on birthweight [31, 37] Decreases in *P. falciparum* transmission across the continent have been insufficient to translate into significant decreases in the number of pregnancies requiring IPTp, while IPTp coverage continues to lag [38].

Our estimates suggest there were 35.1M more pregnancies at risk of *P. falciparum* and 7.7M fewer pregnancies at risk of *P. vivax* in 2020 than were estimated by the previous global estimates for 2007 [20]. These 2007 estimates used MAP transmission limits, separating pregnancies by unstable or stable transmission. The more recent MAP prevalence estimates allowed us to stratify at risk pregnancies by prevalence in more detail than just stable/unstable, and the use of WorldPop estimates of numbers of pregnancies at $5^{km}$ resolution enable us to estimate number of pregnancies, and the level of malaria transmission within which they reside, at a much finer geographic resolution than was applied to 2007 estimates [20]. The World Malaria Report of 2021 estimated that 33 8M pregnancies were at risk of moderate to high *P. falciparum* transmission in sub-Saharan Africa in 2020 [11], one million fewer than our estimate for the same year.

Our analyses have limitations. In the absence of malaria prevalence estimates specifically for pregnant women, we have used *P. falciparum* prevalence estimates generated by MAP for 2 to 10 year-old children. Previous estimates of pregnancies at risk of malaria have used the same metric [20, 38], and literature suggests prevalence among children is representative of

prevalence among pregnant women, especially among primigravidae and in areas of low transmission (<5%) [23]. In the case of *P. vivax*, we used data available from MAP which represents the prevalence across all age groups, the only available global *P. vivax* estimates. Averaging prevalence at the smallest administrative region of each country is pragmatic, however, it means that all pregnancies within an administrative region that has only hot-spots of transmission are classified as being at risk of malaria. As transmission decreases and becomes more localised, a more granular approach to estimating risk of malaria may become more appropriate. Both MAP and WorldPop estimates come with their own limitations and uncertainties. The uncertainty in 2020 MAP estimates is captured in the range between 2.5$^{th}$, mean, and 97.5$^{th}$ percentile prevalence. WorldPop estimates for pregnancies have been computed using the total number of children under one year of age to quantify the number of live births first and then pregnancies. This can result in ecological fallacies as demographic rates at national level are applied to sub-national levels, resulting in possible over- or under-estimation of pregnancies. Similar variability may occur when using defined administrative boundaries to summarise the pregnancies. This is known as the Modifiable Areal Unit Problem (MAUP), which describes how spatial summary measures are inherently influenced by the administrative boundaries that they are reported at [39]. In addition, our estimates of pregnancies at risk of malaria in 2020 do not reflect the seasonality of malaria transmission in some settings. Knowledge of local variation in transmission is important when planning prevention and treatment interventions in areas of highly seasonal transmission. Our estimates are also not stratified by gravidity and so do not allow for estimation of primigravid pregnancies within areas of *P. falciparum* transmission, i.e. those at greatest risk of adverse outcomes.

The Covid-19 pandemic has disrupted malaria control programmes and health systems in general and malaria prevalence and cases greatly increased in 2020 [40, 41]. Indeed, matching the reductions in malaria prevalence over the next two decades may be challenging and the total population at risk of malaria is projected to increase over the coming 50 years [42]. New tools are increasingly available for use in malaria control and elimination, specifically malaria vaccines could increasingly feature in reducing the burden of malaria in pregnancy, potentially in combination with malaria chemoprevention [43]. How these tools may be best deployed to safeguard pregnant women at risk of malaria infection by transmission intensity and malaria species will need to be evaluated.

## Supporting information

**S1 Table. Pregnancies within sub-Saharan Africa at risk of moderate or high (meso-endemic (11–50%) or higher transmission) *Plasmodium falciparum* by year.**
(DOCX)

**S2 Table. Total number of pregnancies at risk of malaria in 2020 and mean (2.5th to 97.5th percentile) prevalence by country and Plasmodium species, disaggregated by stable or unstable transmission.** NB: where Mean (2.5th to 97.5th percentile) prevalence (%) is noted as "<0.001" all three measures of prevalence <0.001%.
(DOCX)

**S3 Table. Pregnancies at risk of *Plasmodium falciparum* and *Plasmodium vivax* in 2020 by regions of the Sustainable Development Goals.**
(DOCX)

**S4 Table. Number of pregnancies at risk of *Plasmodium falciparum* or *P.vivax* by SDG and year.**
(DOCX)

**S1 Fig. Number of pregnancies at risk of *Plasmodium falciparum* in 2020 in two High Burden High Impact Countries: Nigeria and India.**
(TIFF)

**S2 Fig. Number of pregnancies at risk of Plasmodium falciparum in 2020 in each High Burden High Impact Country (except Nigeria and India, see Fig 1).**
(TIFF)

**S3 Fig. Areas at risk of both *Plasmodium falciparum* and *Plasmodium vivax* in 2020.** Note: Map made with Natural Earth. Free vector and raster map data @ naturalearthdata.com.
(TIFF)

**S4 Fig. Change in number of pregnancies at risk of *Plasmodium falciparum* in sub-Saharan Africa by categorical endemicity between 2000 and 2020 (M).**
(TIFF)

**S5 Fig.**
(TIFF)

**S6 Fig. Proportion of pregnancies at risk of *Plasmodium falciparum* within Africa by country from 2000 to 2020.**
(TIFF)

**S7 Fig. Number of pregnancies at risk of *Plasmodium vivax* within Asia by country from 2000 to 2020.**
(TIFF)

**S8 Fig. Proportion of pregnancies at risk of *Plasmodium vivax* within Asia by country from 2000 to 2020.**
(TIFF)

**S9 Fig.** Number (A) and proportion (B) of pregnancies in countries of Plasmodium falciparum and *Plasmodium vivax* transmission globally from 2000 to 2020 disaggregated by risk of malaria or no risk of malaria, and number (C.i) and proportion (C.ii) of pregnancies by risk of *Plasmodium falciparum* and *Plasmodium vivax* (D.i and D.ii) from 2000 to 2020 by geographic region.
(TIFF)

**S10 Fig. Difference in pregnancies at risk of *Plasmodium falciparum*, by categorical endemicity, in 2020 compared to numbers expecting according to 2000 prevalence estimates and 2020 pregnancy estimates 20.**
(TIFF)

**S11 Fig. Proportion of births that are a woman's first birth and total fertility rate per country in sub-Saharan Africa.**
(TIFF)

## Author Contributions

**Conceptualization:** Georgia R. Gore-Langton, Jorge Cano, Patrick G. T. Walker, Matthew E. Cairns, R. Matthew Chico.

**Data curation:** Georgia R. Gore-Langton, Jorge Cano, Hope Simpson, Andrew Tatem, Natalia Tejedor-Garavito, Adelle Wigley, Alessandra Carioli, Peter Gething, Daniel J. Weiss, Patrick G. T. Walker, Matthew E. Cairns, R. Matthew Chico.

**Formal analysis:** Georgia R. Gore-Langton, Jorge Cano, Hope Simpson, Matthew E. Cairns, R. Matthew Chico.

**Methodology:** Jorge Cano, Hope Simpson, Daniel J. Weiss, Patrick G. T. Walker, Matthew E. Cairns, R. Matthew Chico.

**Supervision:** Patrick G. T. Walker, Matthew E. Cairns, R. Matthew Chico.

**Visualization:** Georgia R. Gore-Langton, Hope Simpson, Patrick G. T. Walker, Matthew E. Cairns, R. Matthew Chico.

**Writing – original draft:** Georgia R. Gore-Langton, Hope Simpson, Patrick G. T. Walker, Matthew E. Cairns, R. Matthew Chico.

**Writing – review & editing:** Georgia R. Gore-Langton, Jorge Cano, Hope Simpson, Andrew Tatem, Natalia Tejedor-Garavito, Adelle Wigley, Alessandra Carioli, Peter Gething, Daniel J. Weiss, Daniel Chandramohan, Patrick G. T. Walker, Matthew E. Cairns, R. Matthew Chico.

## References

1. Moore KA, Simpson JA, Scoullar MJL, McGready R, Fowkes FJI. Quantification of the association between malaria in pregnancy and stillbirth: a systematic review and meta-analysis. The Lancet Global Health. 2017; 5(11):e1101–e12. https://doi.org/10.1016/S2214-109X(17)30340-6 PMID: 28967610
2. Menendez C, Ordi J, Ismail MR, Ventura PJ, Aponte JJ, Kahigwa E, et al. The Impact of Placental Malaria on Gestational Age and Birth Weight. The Journal of Infectious Diseases. 2000; 181(5):1740–5. https://doi.org/10.1086/315449 PMID: 10823776
3. Guyatt HL, Snow RW. Impact of malaria during pregnancy on low birth weight in sub-Saharan Africa. Clin Microbiol Rev. 2004; 17(4):760–9. https://doi.org/10.1128/CMR.17.4.760-769.2004 PMID: 15489346
4. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. Lancet (London, England). 2013; 382(9890):417–25. https://doi.org/10.1016/S0140-6736(13)60993-9 PMID: 23746775
5. Guyatt H, Snow R. The epidemiology and burden of Plasmodium falciparum-related anemia among pregnant women in sub-Saharan Africa. The American journal of tropical medicine and hygiene. 2001; 64(1_suppl):36–44. https://doi.org/10.4269/ajtmh.2001.64.36 PMID: 11425176
6. Rogerson SJ, Desai M, Mayor A, Sicuri E, Taylor SM, van Eijk AM. Burden, pathology, and costs of malaria in pregnancy: new developments for an old problem. The Lancet Infectious Diseases. 2018; 18 (4):e107–e18. https://doi.org/10.1016/S1473-3099(18)30066-5 PMID: 29396010
7. Rogerson SJ, Hviid L, Duffy PE, Leke RFG, Taylor DW. Malaria in pregnancy: pathogenesis and immunity. The Lancet Infectious Diseases. 2007; 7(2):105–17. https://doi.org/10.1016/S1473-3099(07)70022-1 PMID: 17251081
8. O'Neil-Dunne I, Achur RN, Agbor-Enoh ST, Valiyaveettil M, Naik RS, Ockenhouse CF, et al. Gravidity-dependent production of antibodies that inhibit binding of Plasmodium falciparum-infected erythrocytes to placental chondroitin sulfate proteoglycan during pregnancy. Infect Immun. 2001; 69(12):7487–92. https://doi.org/10.1128/IAI.69.12.7487-7492.2001 PMID: 11705924
9. Walker PG, Griffin JT, Cairns M, Rogerson SJ, van Eijk AM, ter Kuile F, et al. A model of parity-dependent immunity to placental malaria. Nature communications. 2013; 4:1609. https://doi.org/10.1038/ncomms2605 PMID: 23511473
10. Ma R, Lian T, Huang R, Renn JP, Petersen JD, Zimmerberg J, et al. Structural basis for placental malaria mediated by Plasmodium falciparum VAR2CSA. Nature Microbiology. 2021; 6(3):380–91. https://doi.org/10.1038/s41564-020-00858-9 PMID: 33452495
11. Geneva: World Health Organization. World malaria report 2021. Licence: CC BY-NC-SA 3.0 IGO.
12. Weiss DJ, Lucas TCD, Nguyen M, Nandi AK, Bisanzio D, Battle KE, et al. Mapping the global prevalence, incidence, and mortality of Plasmodium falciparum, 2000–17: a spatial and temporal modelling study. The Lancet. 2019; 394(10195):322–31.

13. Geneva: World Health Organization. WHO Guidelines for malaria, 3 June 2022 (WHO/UCN/GMP/2022.01 Rev.2). License: CC BY-NC-SA 3.0 IGO;. 2022.

14. Allen SJ, Raiko A, O'Donnell A, Alexander NDE, Clegg JB. Causes of preterm delivery and intrauterine growth retardation in a malaria endemic region of Papua New Guinea. Archives of Disease in Childhood—Fetal and Neonatal Edition. 1998; 79(2):F135–F40. https://doi.org/10.1136/fn.79.2.f135 PMID: 9828741

15. Rijken MJ, McGready R, Boel ME, Poespoprodjo R, Singh N, Syafruddin D, et al. Malaria in pregnancy in the Asia-Pacific region. The Lancet Infectious diseases. 2012; 12(1):75–88. https://doi.org/10.1016/S1473-3099(11)70315-2 PMID: 22192132

16. Poespoprodjo JR, Fobia W, Kenangalem E, Lampah DA, Warikar N, Seal A, et al. Adverse pregnancy outcomes in an area where multidrug-resistant plasmodium vivax and Plasmodium falciparum infections are endemic. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2008; 46(9):1374–81.

17. Bardají A, Martínez-Espinosa FE, Arévalo-Herrera M, Padilla N, Kochar S, Ome-Kaius M, et al. Burden and impact of Plasmodium vivax in pregnancy: A multi-centre prospective observational study. PLOS Neglected Tropical Diseases. 2017; 11(6):e0005606. https://doi.org/10.1371/journal.pntd.0005606 PMID: 28604825

18. ter Kuile FO, Rogerson SJ. Plasmodium vivax Infection during Pregnancy: An Important Problem in Need of New Solutions. Clinical Infectious Diseases. 2008; 46(9):1382–4. https://doi.org/10.1086/586744 PMID: 18419440

19. Battle KE, Lucas TCD, Nguyen M, Howes RE, Nandi AK, Twohig KA, et al. Mapping the global endemicity and clinical burden of Plasmodium vivax, 2000–17: a spatial and temporal modelling study. Lancet (London, England). 2019; 394(10195):332–43. https://doi.org/10.1016/S0140-6736(19)31096-7 PMID: 31229233

20. Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. PLoS Med. 2010; 7(1):e1000221. https://doi.org/10.1371/journal.pmed.1000221 PMID: 20126256

21. Pezzulo C, Nilsen K, Carioli A, Tejedor-Garavito N, Hanspal SE, Hilber T, et al. Geographical distribution of fertility rates in 70 low-income, lower-middle-income, and upper-middle-income countries, 2010–16: a subnational analysis of cross-sectional surveys. The Lancet Global Health. 2021; 9(6):e802–e12. https://doi.org/10.1016/S2214-109X(21)00082-6 PMID: 34019836

22. United Nations Depratment of Economic and Social Affairs PD. World Fertility and Family Planning 2020: Highlights. 2020.

23. van Eijk AM, Hill J, Noor AM, Snow RW, ter Kuile FO. Prevalence of malaria infection in pregnant women compared with children for tracking malaria transmission in sub-Saharan Africa: a systematic review and meta-analysis. The Lancet Global Health. 2015; 3(10):e617–e28. https://doi.org/10.1016/S2214-109X(15)00049-2 PMID: 26296450

24. Chico RM, Cano J, Ariti C, Collier TJ, Chandramohan D, Roper C, et al. Influence of malaria transmission intensity and the 581G mutation on the efficacy of intermittent preventive treatment in pregnancy: systematic review and meta-analysis. Tropical Medicine & International Health. 2015; 20(12):1621–33. https://doi.org/10.1111/tmi.12595 PMID: 26325263

25. Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature. 2015; 526(7572):207–11. https://doi.org/10.1038/nature15535 PMID: 26375008

26. James WHM, Tejedor-Garavito N, Hanspal SE, Campbell-Sutton A, Hornby GM, Pezzulo C, et al. Gridded birth and pregnancy datasets for Africa, Latin America and the Caribbean. Scientific Data. 2018; 5:180090. https://doi.org/10.1038/sdata.2018.90 PMID: 29786689

27. Tatem AJ, Campbell J, Guerra-Arias M, de Bernis L, Moran A, Matthews Z. Mapping for maternal and newborn health: the distributions of women of childbearing age, pregnancies and births. International Journal of Health Geographics. 2014; 13(1):2. https://doi.org/10.1186/1476-072X-13-2 PMID: 24387010

28. United Nations DoEaSA, Population Division. World Population Prospects 2019. Highlights (ST/ESA/SER.A/423). 2019.

29. Sedgh G, Singh S, Hussain R. Intended and Unintended Pregnancies Worldwide in 2012 and Recent Trends. Studies in Family Planning. 2014; 45(3):301–14. https://doi.org/10.1111/j.1728-4465.2014.00393.x PMID: 25207494

30. Hay SI, Smith DL, Snow RW. Measuring malaria endemicity from intense to interrupted transmission. The Lancet Infectious diseases. 2008; 8(6):369–78. https://doi.org/10.1016/S1473-3099(08)70069-0 PMID: 18387849

31. Geneva: World Health Organization. Guidelines for malaria, 31 July 2021. Licence: CC BY-NC-SA 3.0 IGO. 2021.

32. World Health Organisation. High burden to high impact: a targeted malaria response. 2018.

33. Vollset SE, Goren E, Yuan C-W, Cao J, Smith AE, Hsiao T, et al. Fertility, mortality, migration, and population scenarios for 195 countries and territories from 2017 to 2100: a forecasting analysis for the Global Burden of Disease Study. The Lancet. 2020; 396(10258):1285–306.

34. Ezeh A, Kissling F, Singer P. Why sub-Saharan Africa might exceed its projected population size by 2100. The Lancet. 2020; 396(10258):1131–3. https://doi.org/10.1016/S0140-6736(20)31522-1 PMID: 32679113

35. Takem EN, D'Alessandro U. MALARIA IN PREGNANCY. Mediterranean Journal of Hematology and Infectious Diseases. 2013; 5(1):e2013010. https://doi.org/10.4084/MJHID.2013.010 PMID: 23350023

36. Twohig KA, Pfeffer DA, Baird JK, Price RN, Zimmerman PA, Hay SI, et al. Growing evidence of Plasmodium vivax across malaria-endemic Africa. PLOS Neglected Tropical Diseases. 2019; 13(1):e0007140. https://doi.org/10.1371/journal.pntd.0007140 PMID: 30703083

37. Roh ME, Kuile FOT, Rerolle F, Glymour MM, Shiboski S, Gosling R, et al. Overall, anti-malarial, and non-malarial effect of intermittent preventive treatment during pregnancy with sulfadoxine-pyrimethamine on birthweight: a mediation analysis. Lancet Glob Health. 2020; 8(7):e942–e53. https://doi.org/10.1016/S2214-109X(20)30119-4 PMID: 32562650

38. Geneva: World Health Organisation. World Malaria Report 2020: 20 years of global progress and challenges. 2020.

39. Fotheringham AS, Wong DWS. The Modifiable Areal Unit Problem in Multivariate Statistical Analysis. Environment and Planning A: Economy and Space. 1991; 23(7):1025–44.

40. Sherrard-Smith E, Hogan AB, Hamlet A, Watson OJ, Whittaker C, Winskill P, et al. The potential public health consequences of COVID-19 on malaria in Africa. Nature Medicine. 2020. https://doi.org/10.1038/s41591-020-1025-y PMID: 32770167

41. Weiss DJ, Bertozzi-Villa A, Rumisha SF, Amratia P, Arambepola R, Battle KE, et al. Indirect effects of the COVID-19 pandemic on malaria intervention coverage, morbidity, and mortality in Africa: a geospatial modelling analysis. The Lancet Infectious Diseases. 2021; 21(1):59–69. https://doi.org/10.1016/S1473-3099(20)30700-3 PMID: 32971006

42. Colón-González FJ, Sewe MO, Tompkins AM, Sjödin H, Casallas A, Rocklöv J, et al. Projecting the risk of mosquito-borne diseases in a warmer and more populated world: a multi-model, multi-scenario intercomparison modelling study. The Lancet Planetary Health. 2021; 5(7):e404–e14. https://doi.org/10.1016/S2542-5196(21)00132-7 PMID: 34245711

43. Greenwood B, Cairns M, Chaponda M, Chico RM, Dicko A, Ouedraogo J-B, et al. Combining malaria vaccination with chemoprevention: a promising new approach to malaria control. Malar J. 2021; 20(1). https://doi.org/10.1186/s12936-021-03888-8 PMID: 34488784