The International Limits and Population at Risk of Plasmodium vivax Transmission in 2009

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Abstract

Background: A research priority for Plasmodium vivax malaria is to improve our understanding of the spatial distribution of risk and its relationship with the burden of P. vivax disease in human populations. The aim of the research outlined in this article is to provide a contemporary evidence-based map of the global spatial extent of P. vivax malaria, together with estimates of the human population at risk (PAR) of any level of transmission in 2009.

Methodology: The most recent P. vivax case-reporting data that could be obtained for all malaria endemic countries were used to classify risk into three classes: malaria free, unstable (<0.1 case per 1,000 people per annum (p.a.)) and stable (≥0.1 case per 1,000 p.a.) P. vivax malaria transmission. Risk areas were further constrained using temperature and aridity data based upon their relationship with parasite and vector biometrics. Medical intelligence was used to refine the spatial extent of risk in specific areas where transmission was reported to be absent (e.g., large urban areas and malaria-free islands). The PAR under each level of transmission was then derived by combining the categorical risk map with a high resolution population surface adjusted to 2009. The exclusion of large Duffy negative populations in Africa from the PAR totals was achieved using independent modelling of the gene frequency of this genetic trait. It was estimated that 2.85 billion people were exposed to some risk of P. vivax transmission in 2009, with 57.1% of them living in areas of unstable transmission. The vast majority (2.59 billion, 91.0%) were located in Central and South East (CSE) Asia, whilst the remainder were located in America (0.16 billion, 5.5%) and in the Africa+ region (0.10 billion, 3.5%). Despite evidence of ubiquitous risk of P. vivax infection in Africa, the very high prevalence of Duffy negativity throughout Central and West Africa reduced the PAR estimates substantially.

Conclusions: After more than a century of development and control, P. vivax remains more widely distributed than P. falciparum and is a potential cause of morbidity and mortality amongst the 2.85 billion people living at risk of infection, the majority of whom are in the tropical belt of CSE Asia. The probability of infection is reduced massively across Africa by the frequency of the Duffy negative trait, but transmission does occur on the continent and is a concern for Duffy positive locals and travellers. The final map provides the spatial limits on which the endemcity of P. vivax transmission can be mapped to support future cartographic-based burden estimations.


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Introduction

The bulk of the global burden of human malaria is caused by two parasites: *Plasmodium falciparum* and *P. vivax*. Existing research efforts have focussed largely on *P. falciparum* because of the mortality it causes in Africa [1,2]. This focus is increasingly regarded as untenable [3–6] because the following factors indicate mortality it causes in Africa [1,2]. This focus is increasingly.

Methods

Analyses Outline

A schematic overview of the analyses is presented in Figure 1. Briefly, *P. vivax* malaria endemic countries (*PvMECs*) were first identified and the following layers were progressively applied within a geographical information system to constrain risk areas and derive the final *P. vivax* spatial limits map: i) a *P. vivax* annual parasite incidence (*PvAPI*) data layer; biological exclusion layers comprising of ii) temperature and iii) aridity data layers; iv) a medical intelligence exclusion layer; and v) a predicted Duffy negativity layer. A detailed description of these steps follows.

Identifying *PvMECs*

Those countries that currently support *P. vivax* transmission were first identified. The primary sources for defining national risk were international travel and health guidelines [25,26] augmented with national survey information, pertinent published sources and personal communication with malariologists. Nations were grouped into three regions, as described elsewhere [19]: i) America; ii) Africa, Saudi Arabia and Yemen (Africa+); and iii) Central and South East (CSE) Asia. To further resolve PAR estimates, the CSE Asia region was sub-divided into West Asia, Central Asia and East Asia (Protocol S1).

Mapping case-reporting data

Methods described previously for mapping the global spatial limits of *P. falciparum* malaria [18] were used to constrain the area defined at risk within the *PvMECs* using *PvAPI* data (the number of confirmed *P. vivax* malaria cases reported per administrative unit per 1,000 people per annum (p.a.)). The *PvAPI* data were obtained mostly through personal communication with individuals and institutions linked to malaria control in each country (Protocol S1).

The format in which these data were available varied considerably between countries. Ideally, the data would be available by administrative unit and by year, with each record presenting the estimated population for the administrative unit and the number of confirmed autochthonous malaria cases by the two main parasite species (*P. falciparum* and *P. vivax*). This would allow an estimation of species-specific API. These requirements, however, were often not met. Population data by administrative unit were sometimes unavailable, in which cases these data were sourced separately or extrapolated from previous years. An additional problem was the lack of parasite species-specific case or API values. In such cases, a parasite species ratio was inferred from alternative sources and applied to provide an estimate of species-specific API. There was, thus, significant geographical variation in the ability to look at the relative frequency of these parasites between areas and this was not investigated further. Finally, although a differentiation between confirmed and suspected cases and between autochthonous and imported cases was often provided, whenever this was not available it was assumed that the cases in question referred to confirmed and autochthonous occurrences.

The aim was to collate data for the last four years of reporting (ideally up to 2009) at the highest spatial resolution available (ideally at the second administrative level (ADMIN2) or higher). A geo-database was constructed to archive this information and link it to digital administrative boundaries of the world available from the 2009 version of the Global Administrative Unit Layers (GAUL) data set, implemented by the Food and Agriculture Organization of the United Nations (FAO) within the EC FAO Food Security for Action Programme [27]. The *PvAPI* data were averaged over the period available and were used to classify areas...
as malaria free, unstable (≤0.1 case per 1,000 p.a.) or stable (≥0.1 case per 1,000 p.a.) transmission, based upon metrics advised during the Global Malaria Eradication Programme [28–30]. These data categories were then mapped using ArcMAP 9.2 (ESRI 2006).

**Biological masks of exclusion of risk**

To further constrain risk within national territories, two “masks” of biological exclusion were implemented [Protocol S2]. First, risk was constrained according to the relationship between temperature and the duration of sporogony, based upon parameters specific to *P. vivax* [31]. Synoptic mean, maximum and minimum monthly temperature records were obtained from 30-arcsec (~1 × 1 km) spatial resolution climate surfaces [32]. For each pixel, these values were converted, using spline interpolation, to a continuous time series representing a mean temperature profile across an average year. Diurnal variation was represented by adding a sinusoidal component to the time series with a wavelength of 24 hours and the amplitude varying smoothly across the year determined by the difference between the monthly

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**Figure 1. Flow chart of the various data and exclusion layers used to derive the final map.** The pink rectangle denotes the surface area and populations of *Pv*MECs, whilst the pink ovoid represents the resulting trimmed surface area and PAR after the exclusion of risk by the various input layers, denoted by the blue rhomboids. Orange rectangles show area and PAR exclusions at each step to illustrate how these were reduced progressively. The sequence in which the exclusion layers are applied does not affect the final PAR estimates.

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Medical intelligence modulation of risk

Medical intelligence contained in international travel and health guidelines [25,26] was used to inform risk exclusion and down-regulation in specific urban areas and sub-national territories, which are cited as being free of malaria transmission (Protocol S3). Additional medical intelligence and personal communication with malaria experts helped identify further sub-national areas classified as malaria free in Cambodia, Vanuatu and Yemen. Specified urban areas were geo-positioned and their urban extents were identified using the Global Urban Mapping Project (GRUMP) urban extents layer [40]. Rules of risk modulation within these urban extents were as follows: i) risk within urban extents falling outside the range of the urban vector An. stephensi [41] (Protocol S3) was excluded; ii) risk within urban areas inhabited by An. stephensi was down-regulated by one level from stable to unstable and from unstable to free (Protocol S3). Specified sub-national territories were classified as malaria free if not already identified as such by the P+API layer and the biological masks. These territories were mapped using the GAUL data set [27].

Duffy negativity phenotype

Since Duffy negativity provides protection against infection with P. vivax [42], a continuous map of the Duffy negativity phenotype was generated from a geostatistical model fully described elsewhere (Howes et al., manuscript in preparation). The model was informed by a database of Duffy blood group surveys assembled from thorough searches of the published literature and supplemented with unpublished data by personal communication with relevant authors. Sources retrieved were added to existing Duffy blood group survey databases [43,44]. The earliest inclusion date for surveys was 1950, when the Duffy blood group was first described [45].

To model the Duffy system and derive a global prediction for the frequency of the homozygous Duffy negative phenotype (Fy(a-b-)), which is encoded by the homozygous FY*RES/FY*RES genotype, the spatially variable frequencies of the two polymorphic loci determining Duffy phenotypes were modelled: i) nucleotide −33 in the gene’s promoter region, which defines positive/negative expression (T-33C); ii) the coding region locus (G125A) determining the antigen type expressed: Fy^a or Fy^b [46]. Due to the wide range of diagnostic methods used to describe Duffy blood types in recent decades, data were recorded in a variety of forms, each providing differing information about the frequency of variants at both loci. For example, some molecular studies sequenced only the gene’s promoter region, and thus could not inform the frequency of the coding region variant; serological diagnoses only testing for the Fy^a antigen could not distinguish Fy^b from the Duffy negative phenotype. As part of the larger dataset, however, these incomplete data types can indirectly inform frequencies of negativity. Therefore, despite only requiring information about the promoter locus to model the negativity phenotype, variant frequencies at both polymorphic sites were modelled. This allowed the full range of information contained in the dataset to be used rather than just the subset specifically reporting Duffy negativity frequencies.

The model’s general architecture and Bayesian framework will be described elsewhere (Howes et al., manuscript in preparation). Briefly, the dataset of known values at fixed geographic locations was used to predict expression frequencies at each locus in all geographic sites where no data were available, thereby generating continuous global surfaces of the frequency of each variant. From the predicted frequency of the promoter region variant encoding null expression (-33C), a continuous frequency map of the Duffy negative population was derived.

Estimating the population at risk of P. vivax transmission

The GRUMP beta version provides gridded population counts and population density estimates for the years 1990, 1995, and 2000, both adjusted and unadjusted to the United Nations’ national population estimates [40]. The adjusted population counts for the year 2000 were projected to 2009 by applying national, medium variant, urban and rural-specific growth rates by country [47]. These projections were undertaken using methods described previously [48], but refined with urban growth rates being applied solely to populations residing within the GRUMP
urban extents, while the rural growth rates were applied to the remaining population. This resulted in a 2009 population count surface of approximately 1 x 1 km spatial resolution, which was used to extract PAR figures. The PAR estimates in Africa were corrected for the presence of the Duffy negativity phenotype by multiplying the extracted population by [1 - frequency of Duffy negative individuals].

Results

Plasmodium vivax malaria endemic countries

A total of 109 potentially endemic countries and territories listed in international travel and health guidelines were identified [25,26]. Ten of these countries: Algeria, Armenia, Egypt, Jamaica (P. falciparum only), Mauritius, Morocco, Oman, Russian Federation, Syrian Arab Republic and Turkmenistan have either interrupted transmission or are extremely effective at dealing with minor local outbreaks. These nations were not classified as PvMECs and are all considered to be in the elimination phase by the Global Malaria Action Plan [24]. Additionally, four malaria endemic territories report P. falciparum transmission only: Cape Verde [49], the Dominican Republic [50], Haiti [50,51] and Mayotte [52]. This resulted in a global total of 95 PvMECs.

Figure 1 summarises the various layers applied on the 95 PvMECs in order to derive the limits of P. vivax transmission. The results of these different steps are described below.

Defining the spatial limits of P. vivax transmission at sub-national level

PvAPI data were available for 51 countries. Data for four countries were available up to 2009. For 29 countries the last year of reporting was 2008, whilst 2007 and 2006 were the last years available for 11 and six countries, respectively. For Colombia the last reporting year was 2005. No HMIS data could be obtained for Kyrgyzstan and Uzbekistan, for which information contained in the most recent travel and health guidelines [23,26] was used to map risk. With the exception of Namibia, Saudi Arabia, South Africa and Swaziland, which were treated like all other nations, no HMIS data were solicited for countries in the Africa+ region, where stable risk of P. vivax transmission was assumed to be present throughout the country territories. In Botswana, stable risk was assumed in northern areas as specified by travel and health guidelines [25,26]. Amongst those countries for which HMIS data were available, 16 reported at ADMIN1 and 29 at ADMIN2 level. For Southern China, Myanmar, Nepal and Peru, data were available at ADMIN3 level. Data for Namibia and Venezuela were resolved at ADMIN1 and ADMIN2 levels. In total, 17,591 administrative units were populated with PvAPI data. Protocol S1 describes these data in detail.

Biological masks to refine the limits of transmission

Figure 3 shows the limits of P. vivax transmission after overlaying the temperature mask on the PvAPI surface. The P. vivax-specific temperature mask was less exclusive of areas of risk than that derived for P. falciparum [18]. Exclusion of risk was mainly evident in the Andes, the southern fringes of the Himalayas, the eastern fringe of the Tibetan plateaux, the central mountain ridge of New Guinea and the East African, Malagasy and Afghan highlands. There was a remarkable correspondence between PvAPI defined risk in the Andean and Himalayan regions and the temperature mask, which trimmed pixels of no risk at very high spatial resolution in these areas.

The aridity mask used here [36] was more contemporary and derived from higher spatial resolution imagery than the one used to define the limits of P. falciparum [18]. Figure 4 shows that the

Figure 2. Plasmodium vivax malaria risk defined by PvAPI data. Transmission was defined as stable (red areas, where PvAPI $\geq 0.1$ per 1,000 people p.a.), unstable (pink areas, where PvAPI $< 0.1$ per 1,000 p.a.) or no risk (grey areas). The boundaries of the 95 countries defined as P. vivax endemic are shown. doi:10.1371/journal.pntd.0000774.g002
effects of the aridity mask were more evident in the Sahel and southern Saharan regions, as well as the Arabian Peninsula. In the western coast of Saudi Arabia, unstable risk defined by the \( P_v \)API layer was reduced to isolated foci of unstable risk by the aridity mask. In Yemen, stable risk was constrained to the west coast and to limited pockets along the southern coast. Similarly, endemic areas of stable risk defined by \( P_v \)API data in southern Afghanistan, southern Iran and throughout Pakistan were largely reduced to unstable risk by the aridity mask.

Medical intelligence used to refine risk

The two international travel and health guidelines consulted [25,26] cite 59 specific urban areas in 31 countries as being malaria free, in addition to urban areas in China, Indonesia (those
found in Sumatra, Kalimantan, Nusa Tenggara Barat and Sulawesi) and the Philippines (Protocol S3). A total of 42 of these cities fell within areas classified as malarious and amongst these, eight were found within the range of An. stephensi, as were some urban areas in south-western Yunnan, China. Risk in the latter was down-regulated from stable to unstable and from unstable to free due to the presence of this urban vector. In the remaining 34 cities and other urban areas in China, Indonesia and the Philippines, risk was excluded. In addition, 36 administrative units, including islands, are cited as being malaria free (Protocol S3). These territories were excluded as areas of risk, if not already classified as such by the PvAPI surface and biological masks. In addition, the island of Aneityum, in Vanuatu [53], the area around Angkor Watt, in Cambodia, and the island of Socotra, in Yemen [54], were classified as malaria free following additional medical intelligence and personal communication with malaria experts from these countries.

Frequency of Duffy negativity

From the assembled library of references, 821 spatially unique Duffy blood type surveys were identified. Globally the data points were spatially representative, with 265 in America, 213 in Africa+ (167 sub-Saharan), 207 in CSE Asia and 136 in Europe. The total global sampled population was 131,187 individuals, with 24,816 (18.9%) in Africa+ and 33 African countries represented in the final database.

The modelled global map of Duffy negativity (Figure 5) indicates that the P. vivax resistant phenotype is rarely seen outside of Africa, and, when this is the case, it is mainly in localised New World migrant communities. Within Africa, the predicted prevalence was strikingly high south of the Sahara. Across this region, the silent Duffy allele was close to fixation in 31 countries with 95% or more of the population being Duffy negative. Frequencies fell sharply into southern Africa and into the Horn of Africa. For instance, the frequency of Duffy negativity in the South African population was 62.7%, increasing to 65.0% in Namibia and 73.5% across Madagascar. The situation was predicted to be highly heterogeneous across Ethiopia, with an estimated 50.0% of the overall population being Duffy negative.

Populations at risk of P. vivax transmission

The estimated P. vivax endemic areas and PAR for 2009 are presented in Table 1, stratified by unstable (PvAPI<0.1 per 1,000 p.a.) and stable (PvAPI≥0.1 per 1,000 p.a.) risk of transmission, globally and by region and sub-region. It was estimated that there were 2.85 billion people at risk of P. vivax transmission worldwide in 2009, the vast majority (91.0%) inhabiting the CSE Asia region, 5.5% living in America and 3.4% living in Africa+, after accounting for Duffy negativity. An estimated 57.1% of the P. vivax PAR in 2009 lived in areas of unstable transmission, with a population of 1.63 billion.

Country level PAR estimates are provided in Protocol S4. The ten countries with the highest estimated PAR, in descending order, were: India, China, Indonesia, Pakistan, Viet Nam, Philippines, Brazil, Myanmar, Thailand and Ethiopia. PAR estimates in India accounted for 41.9% of the global PAR estimates, with 60.3% of the more than one billion PAR (1.19 billion) living in stable transmission areas. The situation in China was different as, according to the PvAPI input data, areas of stable transmission were only found in the southern provinces of Yunnan and Hainan, and in the north-eastern province of Anhui, which reported an unusually high number of cases up to 2007. The latter is in accordance with a recent report documenting the resurgence of malaria in this province [55]. Transmission in the rest of China was largely negligible, with PvAPI values well below 0.1 case per 1,000 people p.a. Given the reported cases, however, these were classified as unstable transmission areas and the total PAR estimated within them, after urban exclusions, was 583 million.
people. All other countries reporting the highest PAR were in CSE Asia, with the exception of Brazil and Ethiopia.

Discussion

We present a contemporary evidence-based map of the global distribution of \textit{P. vivax} transmission developed from a combination of mapped sub-national HMIS data, biological rules of transmission exclusion and medical intelligence. The methods used were developed from those implemented for \textit{P. falciparum} malaria \cite{18} and can be reproduced following the sequence of data layer assemblies and exclusions illustrated in Figure 1.

\textit{Plasmodium vivax} is transmitted within 95 countries in tropical, sub-tropical and temperate regions, reaching approximately 43 degrees north in China and approximately 30 degrees south in Southern Africa. The fact that \textit{P. vivax} has a wider range than \textit{P. falciparum} \cite{18} is facilitated by two aspects of the parasite’s biology \cite{56,31}: i) its development at lower temperatures during sporogony and ii) its ability to produce hypnozoites during its life cycle in the human host \cite{57,18}. The sporogonic cycle of \textit{P. vivax} is shorter (i.e. a lower number of degree days required for its completion) and the parasite’s sexual stage is active at lower temperatures than other human malaria parasites (Protocol S2) \cite{31}. Consequently, generation of sporozoites is possible at higher altitudes and more extreme latitudes. In the human host, hypnozoites of \textit{P. vivax} temperate strains can relax anywhere between months and years after the initial infection, often temporally coincident with optimal climatic conditions in a new transmission season \cite{10,57}.

The resulting maps produced an estimate of 2.85 billion people living at risk of \textit{P. vivax} malaria transmission in 2009. The distribution of \textit{P. vivax} PAR is very different from that of \textit{P. falciparum} \cite{18}, due to the widespread distribution of \textit{P. vivax} in Asia, up to northern China, and the high prevalence of the Duffy negativity phenotype in Africa. China accounts for 22.0% of the global estimated \textit{P. vivax} PAR, although 93.1% of these people live in areas defined as unstable transmission (Protocol S4). An important caveat is that \textit{P}v\textit{API} data from central and northern China could only be accessed at the lowest administrative level (ADMINI) (Protocol S1). The very high population densities found in this country exacerbate the problem, inevitably biasing PAR estimates, despite urban areas in China being excluded from the calculations following information from the sources of medical intelligence that were consulted \cite{25,26}. Malaria transmission in most of these unstable transmission areas in China is probably negligible given the very few cases reported between 2003 and 2007. It is important to stress the necessity to access \textit{P}v\textit{API} data at a higher spatial resolution from China (i.e. at the county level) in order to refine these estimates and minimise biases.

### Table 1. Regional and global areas and PAR of \textit{Plasmodium vivax} malaria in 2009.

<table>
<thead>
<tr>
<th>Region</th>
<th>Area (km$^2$)</th>
<th>PAR (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstable</td>
<td>Stable</td>
</tr>
<tr>
<td></td>
<td>Unstable</td>
<td>Stable</td>
</tr>
<tr>
<td>Africa+</td>
<td>4,812,618</td>
<td>17,980,708</td>
</tr>
<tr>
<td>America</td>
<td>1,368,380</td>
<td>8,087,335</td>
</tr>
<tr>
<td>CSE Asia</td>
<td>5,848,939</td>
<td>6,127,549</td>
</tr>
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<td>West Asia</td>
<td>2,007,247</td>
<td>2,800,612</td>
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<td>Central Asia</td>
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<td>East Asia</td>
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<tr>
<td>World</td>
<td>12,029,937</td>
<td>32,195,600</td>
</tr>
</tbody>
</table>

*The cited references mostly document import cases from Africa. Evidence of transmission of \textit{P. vivax} in Guinea Bissau and Swaziland could not be found in the published literature.*

doi:10.1371/journal.pntd.0000774.t001

### Table 2. Published evidence of \textit{Plasmodium vivax} malaria transmission in African countries.

<table>
<thead>
<tr>
<th>Country</th>
<th>References*</th>
</tr>
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<tbody>
<tr>
<td>Angola</td>
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</tr>
<tr>
<td>Benin</td>
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<td>Burundi</td>
<td>\cite{70–73}</td>
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<tr>
<td>Cameroon</td>
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<td>Equatorial Guinea</td>
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<tr>
<td>Tanzania</td>
<td>\cite{68–72,76,77,79}</td>
</tr>
<tr>
<td>Zambia</td>
<td>\cite{69–72,78,96}</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>\cite{68,69,71}</td>
</tr>
</tbody>
</table>

*The cited references mostly document import cases from Africa. Evidence of transmission of \textit{P. vivax} in Guinea Bissau and Swaziland could not be found in the published literature.*

doi:10.1371/journal.pntd.0000774.t002
In Africa, the modelled prevalence of Duffy negativity shows that very high rates of this phenotype are present in large swaths of West and Central Africa (Figure 3). One of the functions of the Duffy antigen is being a receptor of *P. vivax* [46] and its absence has been shown to preclude infection with this parasite [58,59], although the extent of this has been questioned [60–63]. There is no doubt that the African continent has a climate highly conducive to *P. vivax* transmission (Protocol S2). Moreover, dominant African *Anopheles* have been shown to be competent vectors of this parasite [62,64,65]. In addition, there is a plethora of evidence of *P. vivax* transmission in Africa, mostly arising from travel-acquired *P. vivax* infections during visits to malaria endemic African countries (Table 2; Protocol S1). This evidence supports the hypothesis that *P. vivax* may have been often misdiagnosed as *P. falciparum* in the region due to a combination of morphological similarity and the prevailing bio-geographical dogma driven by the high prevalence of Duffy negativity [60]. Despite the fact that the risk of *P. vivax* is cosmopolitan, PAR estimates in Africa were modulated according to the high limitations placed on infection by the occurrence of the Duffy negative trait. Consequently, the PAR in the Africa+ region accounts for only 3.5% of the global estimated *P. vivax* PAR. Although recent work has shown 42 *P. vivax* infections amongst 476 individuals genotyped as Duffy negative across eight sites in Madagascar [63], we have taken a conservative approach and consider it premature to relax the Duffy exclusion of PAR across continental Africa until this study has been replicated elsewhere.

Mapping the distribution of *P. vivax* malaria has presented a number of unique challenges compared to *P. falciparum*, some of which have been addressed by the methods used here. The influence of climate on parasite development has been allowed for by implementing a temperature mask parameterised specifically for the *P. vivax* life cycle. The question of Duffy negativity and *P. vivax* transmission has also been addressed by modelling the distribution of this phenotype and by allowing the predicted prevalence to modulate PAR. It is also worth noting that the accuracy of HMIS for *P. vivax* clinical cases, particularly in areas of coincidental *P. falciparum* risk, is notoriously poor [66], in part because microscopists are less likely to record the presence of a parasite assumed to be clinically less important. Here, HMIS data were averaged over a period of up to four years and used to differentiate malaria free areas from those that are malariaous. Within the latter, a conservative threshold was applied to classify risk areas as being of unstable (P-API=0.1 per 1,000 p.a.) or stable (P-API=0.1 per 1,000 p.a.) transmission [29]. We believe that this conservative use of HMIS data balances, to some extent, anomalies introduced by *P. vivax* underreporting and the correspondence of the biological masks and P-API data in many areas is reassuring.

The intensity of transmission within the defined stable limits of *P. vivax* risk will vary across this range and this will be modelled using geostatistical techniques similar to those developed recently for *P. falciparum* [19]. This modelling work will be cognisant of the unique epidemiology of *P. vivax*. First, in areas where *P. vivax* infection is coincidental with *P. falciparum*, prevalence of the former may be suppressed by cross-species immunity [67] or underestimated by poor diagnostics [66]. Second, there is the ability of *P. vivax* to generate hypnozoites that lead to relapses. These characteristics render the interpretation of prevalence measures more problematic [5]. Third, the prevalence of Duffy negativity provides protection against infection in large sections of the population in Africa [58,59]. An appropriate modelling framework is under development and will be the subject of a subsequent paper mapping *P. vivax* malaria endemicity using parasite prevalence data. These data are being collated in the MAP database, with nearly 9,000 *P. vivax* parasite rate records archived by 01 March 2010.

**Supporting Information**

**Protocol S1** Defining risk of transmission of *Plasmodium vivax* using case reporting data. Document describing more extensively one of the layers used to create the final map. Found at: doi:10.1371/journal.pntd.0000774.s001 (2.87 MB DOC)

**Protocol S2** Defining the global biological limits of *Plasmodium vivax* transmission. Document describing more extensively two of the layers used to create the final map. Found at: doi:10.1371/journal.pntd.0000774.s002 (0.42 MB DOC)

**Protocol S3** Risk modulation based upon medical intelligence. Document describing more extensively one of the layers used to create the final map. Found at: doi:10.1371/journal.pntd.0000774.s003 (0.36 MB DOC)

**Protocol S4** Country level area and population at risk of *Plasmodium vivax* malaria in 2009. Country-level table of the estimated area and populations at risk of *P. vivax* malaria in 2009. Found at: doi:10.1371/journal.pntd.0000774.s004 (0.16 MB DOC)

**Acknowledgments**

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**Author Contributions**

Conceived and designed the experiments: SIH. Performed the experiments: CAG REH APP PWG TPVB WHT. Analyzed the data: CAG. Contributed reagents/materials/analysis tools: REH APP PWG TPVB WHT. Wrote the paper: CAG SIH.

References


PROTOCOL S1: Defining risk of transmission of *Plasmodium vivax* using case reporting data

**Identification of *Plasmodium vivax* malaria endemic countries**

In order to define *Plasmodium vivax* malaria endemic countries (PvMECs), two sets of international travel and health guidelines [1,2] were used to list all countries potentially supporting some level of *P. vivax* transmission. This yielded 109 countries in the three regions: America (22 countries), the Africa+ region (African countries plus Yemen and Saudi Arabia, due to the presence of *Anopheles arabiensis*) (52 countries) and Central and South East (CSE) Asia (35 countries).

Nineteen PvMECs were identified in America. All countries in Mesoamerica and South America are *P. vivax* endemic, except for Uruguay and Chile. There is no *P. vivax* transmission in the Caribbean, where the only two malaria endemic countries, Dominican Republic and Haiti, report *P. falciparum* transmission only [3,4]. The very limited risk found in Jamaica after an outbreak in 2006/7 [5] was also exclusively due to *P. falciparum*.

All 22 countries with *P. falciparum* malaria endemicity in CSE Asia are also *P. vivax* endemic. Eight countries towards the more temperate zones of Eastern Europe and Central Asia report only *P. vivax* transmission at present. These countries are, from West to East, Turkey, Georgia, Azerbaijan, Iraq, Uzbekistan, Kyrgyzstan, Korea Democratic People’s Republic (DPR) and the Republic of Korea. Armenia, Syrian Arab Republic and Turkmenistan have not reported locally transmitted *P. vivax* malaria cases in recent years and were thus not classified as currently *P. vivax* endemic, although none have received “certification of eradication” by the World Health Organization [6]. In Oman, four cases were reported in Manah district in 2007 and eight in Sohar district in 2008 (Al-Zedjali, pers. comm.) after the interruption, in 2003, of sporadic transmission [2]. Oman, therefore, was not classified as a PvMEC. In the Russian Federation, very limited risk of *P. vivax* transmission is reported in areas of intense migration [2] and it was, therefore, not considered a PvMEC.

The high prevalence of the Duffy negativity phenotype in indigenous populations of Africa, particularly of Central and West Africa, has led to the dogma that *P. vivax* is absent from large areas of the continent. Climatic conditions in most of Africa, however, are favourable to the completion of the sporogonic cycle of *P. vivax* and African anophelines have been shown to be receptive to this parasite [7]. Moreover, recent reports show that Duffy negativity does not necessarily confer complete protection against *P. vivax* infection [8-10]. Apart from the well documented transmission of *P. vivax* in countries of the Horn of Africa, published evidence confirms that *P. vivax* transmission is present in several countries of the continent, including
Angola [11], Democratic Republic of the Congo [12], Equatorial Guinea [13], Madagascar [14-17], Mauritania [18], Republic of the Congo [19] and São Tomé and Príncipe [20]. Evidence also exists of *P. vivax* infections imported to non-endemic countries from many African countries. In France, 275 imported *P. vivax* cases from Africa were recorded between 1995 and 1998 [21]. The origin of these cases included countries in West Africa (n=45), Central Africa (n=28), East and South Africa (n=22) and the Indian Ocean Islands (n=180). A large retrospective analysis of *P. vivax* malaria imported to Europe showed that 11.4% and 5.5% of 618 cases originated in West and Central Africa, respectively [22]. Other reports have documented *P. vivax* importation from Equatorial Guinea [23], Mozambique [24] and Somalia [25-27]. Lastly, the latest Centers for Disease Control and Prevention (CDC) traveller’s health book features *P. vivax* amongst the malaria parasite species responsible for infections in most African countries, with frequencies ranging from rare to 15% [1].

Based on the reviewed evidence, a total of 46 countries and territories in Africa+ were classified as *PvMECs*. Exceptions were Cape Verde and Mayotte, where only *P. falciparum* transmission is documented to exist [28,29], as well as Algeria, Egypt, Morocco and Mauritius, all of which have previously been malaria endemic but are presently classified as malaria free or with no indigenous transmission in recent years by the two sets of travel and health guidelines consulted [1,2]. Figure 1 shows the 95 countries classified as *PvMECs* and Table 1 lists them by region and sub-region.

**Protocol S1, Figure 1.** *PvMECs* by region: America (yellow), Africa+ (green) and CSE Asia (dark blue, West Asia; middle blue, Central Asia; light blue, East Asia).
Protocol S1, Table 1. *PvMECs* by regions and sub-regions as per Figure 1.

<table>
<thead>
<tr>
<th>Africa+</th>
<th>America</th>
<th>CSE Asia</th>
</tr>
</thead>
<tbody>
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<td>West Asia</td>
</tr>
<tr>
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<td>Belize</td>
<td>Afghanistan</td>
</tr>
<tr>
<td>Botswana</td>
<td>Bolivia</td>
<td>Azerbaijan</td>
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<td>Burkina Faso</td>
<td>Brazil</td>
<td>Bangladesh</td>
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<tr>
<td>Burundi</td>
<td>Colombia</td>
<td>Bhutan</td>
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<tr>
<td>Cameroon</td>
<td>Costa Rica</td>
<td>Georgia</td>
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<tr>
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<td>India</td>
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<td>Chad</td>
<td>El Salvador</td>
<td>Iran</td>
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<td>Comoros</td>
<td>French Guiana</td>
<td>Iraq</td>
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<tr>
<td>Congo</td>
<td>Guatemala</td>
<td>Kyrgyzstan</td>
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<td>Côte d’Ivoire</td>
<td>Guyana</td>
<td>Nepal</td>
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<td>Congo (DR)</td>
<td>Honduras</td>
<td>Pakistan</td>
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<td>Mexico</td>
<td>Sri Lanka</td>
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<td>Nicaragua</td>
<td>Tajikistan</td>
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<td>Panama</td>
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<td>Ethiopia</td>
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<td>Korea, DPR</td>
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<td>Mali</td>
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<td>Namibia</td>
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<td>Rwanda</td>
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<td>Philippines</td>
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<td>São Tomé and Príncipe</td>
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<td>Solomon Islands</td>
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<td>Saudi Arabia</td>
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<td>Timor-Leste</td>
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<td>Uganda</td>
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<td>Yemen</td>
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<td>Zimbabwe</td>
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Classification of risk based on *P. vivax* annual parasite incidence data

In order to classify risk areas of *P. vivax* transmission, methodologies used to map the spatial limits of *P. falciparum* transmission described previously [30] were adapted for *P. vivax*. Areas of extremely low, unstable transmission of *P. vivax* were assigned to administrative units reporting an annual parasite incidence (PvAPI) of less than 0.1 case per 1,000 population per annum (p.a.), whilst those reporting a PvAPI of ≥0.1 case per 1,000 population p.a. were classified as being of stable transmission. This criterion was found to be a reliable indicator for the cessation of indoor residual spraying during the consolidation phase of the Global Malaria Eradication Programme [31-33]. During this period, the limit was reduced from 0.5‰ as it became recognized that surveillance, including passive and active case detection, was often less accurate and reliable than nations thought: malaria often resumed after the cessation of spraying from 0.5‰, but rarely from 0.1‰. This more conservative categorization of malaria transmission also helps compensate for the vagaries of sub-national level case reporting [34-36].

**PvAPI data used**

Table 2 summarizes PvAPI data characteristics for all PvMECs for which these were available. API data were not available for any country in the Africa+ region, with the exception of Namibia, Saudi Arabia and South Africa. Unfortunately, case-reporting data for South Africa and Namibia did not discriminate between parasite species; it was assumed that risk of transmission of *P. vivax* and *P. falciparum* were equal across the mapped administrative units. Maps of confirmed cases by district in Swaziland for the years 2007-2009 were used to infer risk categories, assuming equal level of risk of transmission for *P. falciparum* and *P. vivax*. For Botswana, risk was constrained at the first administrative (ADMIN1) level using information contained in the travel and health guidelines consulted [1,2], assuming stable risk in malaria transmission areas. For other countries in this region, stable risk of *P. vivax* transmission was assumed to be present throughout their territories.

Case reporting data were not available either for Kyrgyzstan or Uzbekistan. In these countries, risk was defined at ADMIN1 and ADMIN2 levels, respectively, from information available in international travel and health guidelines [1,2].

In total, API data were not available for 44 identified PvMECs. Most data for the other 51 countries were obtained through personal communication with individuals and institutions linked to malaria control in each country. The aim was to collate data for the four last years of reporting, ideally up to 2009. For four countries the last year of reporting available was 2009. For 29 countries, 2008 was the last year of reporting available, whilst 2007 and 2006 were the
last years available for 11 and six countries, respectively. For Colombia, risk data were not available after 2005. In terms of the length of the period of reporting, one year of data was available for 13 countries, two years for four countries, three years for six countries and four years for 28 countries (Table 2).

Regarding the spatial resolution of the PvAPI data, or the administrative level at which case reporting data were available, 16 countries reported at ADMIN1 level and 29 at ADMIN2 level. For southern China, Myanmar, Nepal and Peru, data were available at ADMIN3 level. In central and northern China data were available at ADMIN1 level. Data for Namibia and Venezuela were resolved at a mixture of ADMIN1 and ADMIN2 levels. The best average spatial resolution (ASR) was attained in Swaziland (ASR = 18) and the poorest in Saudi Arabia (ASR = 385). In total, 17,591 administrative units were populated with PvAPI data (Table 2).

**Mapping PvAPI data**

In order to map PvAPI data consistently, they were reconciled to the 2009 version of the Global Administrative Unit Layers (GAUL) data set, implemented by the Food and Agriculture Organization of the United Nations (FAO) within the EC FAO Food Security for Action Programme [37].
Protocol S1, Table 2. Mapped *P. vivax* annual parasite incidence (*PvAPI*) data for the countries for which they could be accessed. The data are grouped by the three global regions defined by Hay et al. [38]: Africa+, America and Central and South East (CSE) Asia. ADMIN1, 2 or 3 refers to the administrative division level (first, second or third level) at which data were available. The number of risk units refers to how many administrative units, at the level specified, were populated with actual data. Year start and Year end mark the start and end of the period for which data were available. ASR is the average spatial resolution of the mapped *PvAPI* data, calculated as: $\sqrt{\text{Country area} / \text{number of *PvAPI* data units mapped}}$. The lower the ASR the better, with values <100 desired for an optimal overall spatial resolution.

<table>
<thead>
<tr>
<th>Region</th>
<th>Country</th>
<th>Administrative level</th>
<th># risk units</th>
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<th>Year end</th>
<th>ASR</th>
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<td>53</td>
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<td>2009</td>
<td>18</td>
<td>[42]</td>
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*Multiple requests to relevant authorities for more recent or higher spatial resolution API data were unsuccessful.*
References

PROTOCOL S2: Defining the global biological limits of *Plasmodium vivax* transmission

The temperature mask

Temperature affects many aspects of mosquito and parasite physiology [1]. One aspect, which is critical for malaria transmission, is the temperature dependence of sporogony: the time required for *Plasmodium vivax* sporozoites to develop in *Anopheles* mosquitoes. A method for estimating the duration of sporogony has been proposed, based on the number of degree-days required by the parasite to complete development [2,3], or the sum of the number of degrees in a day by which the mean temperature exceeds the minimum required for the development of sporozoites. Nikolaev [4] showed that the degree-days required for the maturation of sporozoites in an *An. maculipennis* population from Russia was 105 for *P. vivax*, 111 for *P. falciparum* and 144 for *P. malariae* and that parasite development ceased below 16 °C for *P. falciparum* and *P. malariae* and below 14.5 °C for *P. vivax*. The duration of sporogony (DS) in days can thus be calculated as:

\[ DS = \frac{DD}{T - T_{th}} \]

where *DD* is the parasite species-specific number of degree-days required for sporogony, *T* is the ambient temperature and *T_{th}* is the minimum temperature required for parasite development.

Figure 1 illustrates the implications of the above equation for *P. vivax*, *P. falciparum* and *P. malariae* development in *An. maculipennis* across a range of temperatures. It shows that *P. vivax* is able to develop at the lowest temperatures, followed by *P. falciparum* and *P. malariae*, thus helping explain the species-specific latitudinal and altitudinal limits of the parasites globally [5,6]. The curves never reach a true asymptote on the *y*-axis, but the duration of sporogony becomes so extended that few anophelines will survive long enough to inoculate humans and at 14.5 °C *P. vivax* parasite development ceases entirely. Conversely, as temperature increases, the duration of sporogony decreases and at 30 °C it can take less than ten days. At these high temperatures, the feasibility of sporogony becomes limited by parasite and vector survival, which plummet as mean temperatures rise above 32 °C [7]. The duration of sporogony is dependent fundamentally on enzyme kinetics [8] and thus is widely assumed to be relatively independent of vector species. It is the interplay between the duration of sporogony and the species-specific longevity of the *Anopheles* vector that forms the basis of the temperature mask.
Synoptic mean, maximum, and minimum monthly temperature data were obtained from the WorldClim data resource in the form of 30-arcsec spatial resolution (corresponding approximately to pixels of 1 × 1 km at the equator) climate surfaces [9]. These interpolated climatologies reflect the long-term mean values for the 1950-2000 period and are available globally for each synoptic month, providing a total of 36 surfaces (mean, maximum, and minimum surfaces for each of the 12 months of the year).

Protocol S2, Figure 1. The relationship between temperature and the duration of sporogony. *P. vivax* (blue), *P. falciparum* (yellow) and *P. malariae* (green). The open circle indicates the temperature below which most vectors do not outlive the length of sporogony for *P. vivax*, which corresponds to 31 days at *circa* 18 °C (dotted orange lines). The dashed red line indicates the absolute temperature below which *P. vivax* development ceases (14.5 °C).

The set of 12 monthly mean values available for each 1 × 1 km pixel were converted into a continuous mean temperature time-series using spline interpolation. Diurnal variation was superimposed on this time-series using a sinusoidal function with wavelength = 24 hrs. The amplitude of diurnal variation was determined as half of the difference between spline interpolated maximum and minimum temperature time series, such that the final temperature value T for a given time t was derived as:
Where $T_{mx}$, $T_{mn}$ and $T_{mean}$ are the values of the splined maximum, minimum and mean temperature time series, respectively; $\omega$ is the angular speed ($\pi/12$, for a daytime period); $t$ is the time in hours; and $\varphi$ is the phase, which was set to zero, thus, assuming maximum and minimum temperatures were reached at noon and midnight, respectively. For subsequent calculations, the final curve was discretised into 4,380 units, each representing a time period of two hours.

Because ambient temperatures vary constantly throughout a year, the temperature regime experienced by vectors at a given location will vary according to their emergence date. The limiting effect of temperature on sporogony was estimated at each pixel for 365 separate “cohorts” of vectors, each emerging on a different day of the year and, therefore, experiencing a unique temperature regime throughout their lifespan. The time required to reach sporogony (i.e. the accumulation of 105 degree days) was calculated for each cohort and those for which this duration exceeded the expected lifespan of the dominant vector species were considered unable to support transmission. Those pixels in which no cohorts were able to support transmission were classified as being at zero risk of transmission.

Vector lifespan was defined as 31 days since estimates of the longevity of the main dominant vectors [10] indicate that 99% of anophelines die in less than this time span. The exceptions were areas that support the longer-lived *Anopheles sergentii* and *An. superpictus*, where a lifespan of 62 days was considered more appropriate biologically [11]. Although temperature will affect other parameters of the basic reproduction rate of infection [12], including vector biting and resting habits, it seems reasonable to consider the proportion of the population surviving 31 days as the critical point of interruption of *P. vivax* transmission. To a close approximation, most vector populations would have been reduced to 1% of their original population size within 31 days. With the exception of *An. sergentii* and *An. superpictus*, it is rare for adult dominant vectors of malaria to survive longer than a month, with more than 99% of the average population dying after 31 days. The longer-lived vectors are generally those adapted to survive at higher altitudes or harsher conditions, such as *An. superpictus* and *An. sergentii*. Despite the fact that a relatively small proportion of the populations of these vectors are normally able to survive longer than one month, the number of individuals surviving might still pose a significant risk in terms of malaria transmission by being able to support parasite development at lower temperatures. After 62 days, however, most individuals of both species (>$95\%$) would also have succumbed.
Protocol S2, Figure 2. Areas of *P. vivax* malaria endemic countries (PvMECs) excluded by the temperature mask (dark green pixels). Areas climatically suitable for *P. vivax* transmission are shown in grey, and the remaining non-endemic world is shaded white.

The aridity mask

The ability of adult vectors to survive long enough to contribute to parasite transmission, and of their eggs and larvae to survive in sufficient numbers to sustain transmission, is dependent on the level of ambient humidity and the species-specific ability to withstand arid conditions [13-15]. These potentially limiting conditions prevail in deserts and their fringes found in malaria endemic countries. Extremely arid areas were identified using the global Land Cover product of the GlobCover project (ESA/ESA GlobCover Project, led by MEDIAS-France/POSTEL) [16]. This product is derived from data provided by the Medium Resolution Imaging Spectrometer (MERIS), on board the European Space Agency’s (ESA) ENVIronmental SATellite (ENVISAT) for the period between December 2004 and June 2006 at a spatial resolution of 300 meters. The GlobCover Land Cover product classifies the land surface into 22 classes amongst which the “bare areas” class (pixel value = 200) represents desert biomes. The land cover layer was resampled to 1 × 1 km spatial resolution using a majority filter to match the other layers and was overlaid on top of the temperature mask. The aridity mask worked in a step-wise fashion by which risk was down-regulated one class from its initial value (i.e. stable to unstable and unstable to no risk). Therefore, the only areas where risk was excluded were those where the *PvAPI* layer had already defined unstable risk of malaria.
Protocol S2, Figure 3. The “bare areas” class of the GlobCover Land Cover product (yellow pixels). The mask is depicted within the territories of PvMECs.
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PROTOCOL S3: Risk modulation based upon medical intelligence

Urban transmission

Urban areas are less malarious than the surrounding rural environments due to the distinct ecological conditions presented by man-made environments [1,2]. The extent to which transmission is reduced will vary according to the local Anopheles species. Urbanization has been shown to reduce malaria transmission, measured by the entomological inoculation rate, by an order of magnitude across Africa, due to reduced vector diversity and density, as well as lower anopheline survival, biting and sporozoite rates in urban versus rural areas [1]. Anopheles darlingi, the main malaria vector in America, has shown itself to be similarly unsuited to urban environments [3].

Urban malaria transmission is more entrenched in the Indian subcontinent because of the presence of An. stephensi and, to a lesser extent, An. culicifacies, both recognised urban malaria vectors [4]. No malaria vector is better adapted to urban environments than An. stephensi, and this is due to its ability to breed in all types of artificial collections of water, such as wells, pits, tanks and drains [5]. Anopheles culicifacies is less resilient to man-made environments and is particularly affected by pollution of water sources [5,6]. Importantly, the vector densities and sporozoite rates of both these species have been shown to decrease from peri-urban to urban areas [5,7,8]. Despite this decrease, it is estimated that approximately 8% of reported malaria cases in India come from urban areas [9], with incidence often surpassing the stable risk threshold. Reported annual parasite incidence (API) estimates amongst 86 cities across India in 1993 ranged from 0 to 51.85 cases per 1,000 people per annum (p.a.), with a median of 0.97 [10]. Seventy of these cities would have been classified as supporting stable transmission according to the API threshold used in this paper (i.e. API ≥0.1 case per 1,000 people p.a.). In 2004, the API in an impoverished area located in the outskirts of Kolkata was measured at 1.5 cases per 1,000 residents p.a., with the majority (97%) due to P. vivax [11]. Since An. culicifacies seems to be more affected by the process of urbanisation, it was assumed that urban malaria transmission is maintained mainly by An. stephensi (Figure) as defined by the rules of risk modulation described below.
Risk modulation in specified urban areas

There are 59 cities cited as being malaria free in the two sets of international travel and health guidelines consulted [13,14] (Table 1). In addition, urban areas in China, the Philippines and Indonesia (specifically those located in Sumatra, Kalimantan, Nusa Tenggara Barat and Sulawesi) are said to be malaria free. This is obviously not a comprehensive list of malaria free cities but rather one restricted to main destinations of interest to travellers. Specific cities were geo-positioned and their urban extents were identified using the Global Rural Urban Mapping Project (GRUMP) urban extents layer [15]. In China, the Philippines and specified areas of Indonesia all urban extents were identified and mapped. The resulting layer was overlaid on the PvAPI layer and biological masks to identify the underlying risk of malaria. Those cities falling within the range of An. stephensi [12] were also identified.

Of the 59 specified cities, 17 are in areas where malaria transmission is absent as defined by the PvAPI layer and the biological masks (e.g. highland areas). The urban extents of the remaining 42 cities cover areas defined as unstable or stable transmission or both (Table 1). Only eight of these cities fall within the range of An. stephensi: six in India (Bangalore, Kolkata, Mumbai, Nagpur, Nashik and Pune) and two in Myanmar (Mandalay and Yangon;
Figure). In addition, cities in south-western Yunnan, China, also fall in areas inhabited by this vector.

For all cities falling outside the range of *An. stephensi*, risk was classified as absent throughout their urban extents. For those cities falling within the range of *An. stephensi*, risk was assumed to be one level lower than the surrounding risk defined by *PvAPI* data and the biological masks. This is to allow for the potential transmission of malaria by *An. stephensi* combined with the transmission reducing effects of urban areas [5,7,8].

**Protocol S3, Table 1.** Cities cited as being malaria free by the sources consulted [13,14]. Defined risk refers to the malaria risk categories defined by the *PvAPI* layer and biological masks; note that urban extents often cover more than one category. Modified risk refers to the new malaria risk categories assigned according to the rules described in the text. Cities where the defined risk was “free” were not affected by these rules.

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Risk exclusion in administrative areas

Some sub-national administrative areas and territories are listed as being malaria free by the international travel and health guidelines consulted [13,14]. These are shown in Table 2. Such territories were mapped using the GAUL data set [16] and risk within them was assigned a malaria free category, if not already classified as such by the PvAPI layer and the biological masks. In addition to the territories listed in Table 2, the island of Socotra, in Yemen, has not reported cases since 2005 after malaria elimination activities were initiated in 2000 [17]; this island was assumed to be malaria free. Two further exclusions were those of the island of Aneityum, in Vanuatu [18], and the Angkor Watt area, in Cambodia (corresponding to two districts in Siem Reap province), which were classified as malaria free following personal communication with malaria experts in these countries.

Protocol S3, Table 2. Administrative areas defined as being malaria free by international travel and health guidelines.

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References


PROTOCOL S4: Country level area and population at risk of *Plasmodium vivax* malaria in 2009.

**Protocol S4, Table.** Area and population at risk (PAR) of *Plasmodium vivax* malaria in 2009. Unstable and stable risk correspond to PvAPI <0.1 case per 1,000 people per annum and PvAPI ≥0.1 case per 1,000 per annum, respectively. Total estimated country areas and populations are also listed.

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<th>Country area (km$^2$)</th>
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<th>Country population*</th>
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<td>21,419</td>
<td>142,298</td>
<td>3,093,964</td>
</tr>
<tr>
<td>Region/Country</td>
<td>Risk area (km$^2$)</td>
<td>Country area (km$^2$)</td>
<td>PAR</td>
<td>Country population$^*$</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------</td>
<td>----------------------</td>
<td>-----</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td>Unstable  Stable</td>
<td>Unstable  Stable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>15,246  3,740</td>
<td>782,223  1,268,928</td>
<td>284,329</td>
<td>81,454,747</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>4,319   0</td>
<td>449,909  307,172</td>
<td>0</td>
<td>27,427,706</td>
</tr>
<tr>
<td><strong>World</strong></td>
<td><strong>12,029,937</strong>  <strong>32,195,600</strong></td>
<td><strong>69,516,818</strong>  <strong>1,628,063,132</strong></td>
<td><strong>1,220,960,598</strong></td>
<td><strong>5,911,385,997</strong></td>
</tr>
</tbody>
</table>

*The Global Rural Urban Mapping Project gridded population database beta version population estimates for 2000 are derived through adjustment to United Nations national population total estimates made in the 2004 edition of the World Populations Prospects report. Through the application of separate 2000-2005 and 2005-2010 urban and rural growth rates estimated by the most recent edition available at the time of writing of the United Nations World Urbanization Prospects (2007 edition) to obtain a 2009 population surface, the estimated population totals show some deviations from national population totals estimated by the most recent edition of the UN World Population Prospects report (2008), due to the differences in estimates and methods used between the different reports.