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RESEARCH ARTICLE

A Long Neglected World Malaria Map: *Plasmodium* Endemicity in 2010

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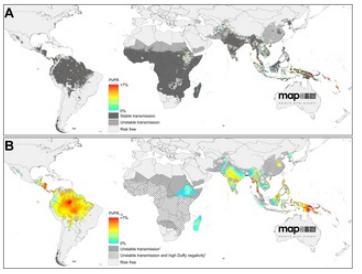
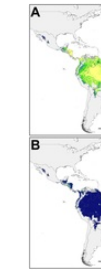
Figures





Abstract

Background

Current understanding of the spatial epidemiology and geographic
Plasmodium vivax is far less developed than that for *P. falciparum*, re
rational strategies for control and elimination. Here we present the
to map the global endemicity of this hitherto neglected parasite.

Methodology and Findings

We first updated to the year 2010 our earlier estimate of the geogr
transmission. Within areas of stable transmission, an assembly of 9
vivax parasite rate (*Pv*PR) surveys collected from 1985 to 2010 were
spatiotemporal Bayesian model-based geostatistical approach to e
age-standardised to the 1–99 year age range ($PvPR_{1-99}$) within eve
grid square. The model incorporated data on Duffy negative pheno
suppress endemicity predictions, particularly in Africa. Endemicity w
relatively narrow range throughout the endemic world, with the poi
exceeding 7% $PvPR_{1-99}$. The Americas contributed 22% of the globa
transmission, but high endemic areas were generally sparsely pop
contributed only 6% of the 2.5 billion people at risk (PAR) globally. In
meant stable transmission was constrained to Madagascar and pa
contributing 3.5% of global PAR. Central Asia was home to 82% of gl
important high endemic areas coinciding with dense populations p
Myanmar. South East Asia contained areas of the highest endemici
Papua New Guinea and contributed 9% of global PAR.

Conclusions and Significance

This detailed depiction of spatially varying endemicity is intended to
needed paradigm shift towards geographically stratified and evide
for *P. vivax* control and elimination.

Author Summary

Plasmodium vivax is one of five parasites causing malaria in humans across a larger swathe of the globe and potentially affects a larger than its more notorious cousin, *Plasmodium falciparum*, it receives a research attention and financing: around 3%. This neglect, coupled more complex nature of vivax biology, means important knowledge our current ability to control the disease effectively. This patchy kno recognised as a cause for concern, in particular as the global comm challenge of malaria elimination which, by definition, includes *P. viva* common Plasmodium species as well as *P. falciparum*. Particularly c absence of an evidence-based map describing the intensity of *P. vi* different parts of the world. Such maps have proved important for c diseases in supporting international policy formulation and regiona planning, implementation, and monitoring. In this study we present effort to map the global endemicity of *P. vivax*. We assembled nearly worldwide in which communities had been tested for the prevalenc Using a spatial statistical model and additional data on environmen Duffy negativity, a blood disorder that protects against *P. vivax*, we e infection prevalence in every 5×5 km grid square across areas at ri provide new insight into the geographical patterns of the disease, h the highest endemicity in South East Asia and small pockets of Ama endemic setting predominating in Africa. This new level of detailed r contribute to a wider shift in our understanding of the spatial epide important parasite.

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Introduction

The international agenda shaping malaria control financing, resear
implementation is increasingly defined around the goal of regional
ambition ostensibly extends to all human malarias, but whilst recen
surge in research attention for *Plasmodium falciparum*, the knowled
major human malaria, *Plasmodium vivax*, is far less developed in alm
[7]–[11]. During 2006–2009 just 3.1% of expenditures on malaria res
development were committed to *P. vivax* [12]. The notion that contro
developed primarily for *P. falciparum* in holoendemic Africa can be t
successfully to *P. vivax* is, however, increasingly acknowledged as i
Previous eradication campaigns have demonstrated that *P. vivax* fre
entrenched long after *P. falciparum* has been eliminated [18]. The p
on the global health agenda has risen further as evidence accumu
some settings to cause severe disease and death [19]–[25], and of
numbers of people living at risk [26].

Amongst the many information gaps preventing rational strategies
elimination, the absence of robust geographical assessments of ris
as particularly conspicuous [9], [27]. The endemic level of the disea
burden on children, adults, and pregnant women; the likely impact
measures; and the relative difficulty of elimination goals. Despite th
importance of these issues, there has been no systematic global as
endemicity. The Malaria Atlas Project was initiated in 2005 with an i
falciparum that has led to global maps [28]–[30] for this parasite bei
policy planning at regional to international levels [4], [31]–[36]. Here
outcome of an equivalent project to generate a comprehensive evi
infections worldwide, and to generate global risk maps for this hithe
We build on earlier work [26] defining the global range of the disea
classifications of populations at risk to now assess the levels of en
these several billion people live. This detailed depiction of geograp
intended to contribute to a much-needed paradigm shift towards ge
and evidence-based planning for *P. vivax* control and elimination.

Numerous biological and epidemiological characteristics of *P. vivax* challenges to defining and mapping metrics of risk. Unlike *P. falcipa* a dormant hypnozoite liver stage that can cause clinical relapse ep periodic events manifest as a blood-stage infection clinically indisti primary infection and constitute a substantial, but geographically v total patent infection prevalence and disease burden within differe [39]–[41]. The parasitemia of *P. vivax* typically occurs at much lower those of falciparum malaria, and successful detection by any given much less likely. Another major driver of the global *P. vivax* landscap the Duffy negativity phenotype [42]. This inherited blood condition of protection against *P. vivax* infection and is present at very high fre majority of African populations, although is rare elsewhere [43]. The others, mean that the methodological framework for mapping *P. viv* interpretation of the resulting maps, are distinct from those already *falciparum* [28], [29]. The effort described here strives to accommod distinctions in developing a global distribution of endemic vivax ma

Methods

The modelling framework is displayed schematically in Figure 1. In b updating of the geographical limits of stable *P. vivax* transmission ba reporting data and biological masks; (ii) assembly of all available *P.* globally; (iii) development of a Bayesian model-based geostatistical endemicity within the limits of stable transmission; and (iv) a model Details on each of these stages are provided below with more exte included as Protocols S1, S2, S3, and S4.

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Figure 1. Schematic overview of the mapping procedures and m *Plasmodium vivax* endemicity.

Blue boxes describe input data. Orange boxes denote models a procedures; green boxes indicate output data (dashed lines rep intermediate outputs and solid lines final outputs). U/R=urban/r Nations Population Prospects. Labels S1-4 denote supplementa Protocols S1, S2, S3, and S4.

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Updating Estimates of the Geographical Limits of Ende

vivax in 2010

The first effort to systematically estimate the global extent of *P. viva* define populations at risk was completed in 2009 [26]. As a first ste we have updated this work with a new round of data collection for t updated data assemblies and methods are described in full in Prot work first involved the identification of 95 countries as endemic for these, *P. vivax* annual parasite incidence (*Pv*API) routine case report from 17,893 administrative units [44]. These *Pv*API and other medica were combined with remote sensing surfaces and biological model areas where extreme aridity or temperature regimes would limit or (see Protocol S1). These components were combined to classify the to experience zero, unstable (*Pv*API <0.1‰ per annum), or stable (*P* annum) *P. vivax* transmission. Despite the very high population frequ negativity across much of Africa, the presence of autochthonous tr has been confirmed by a systematic literature review for 42 African therefore treated Africa in the same way as elsewhere in this initial deemed to have stable *P. vivax* transmission unless the biological m data suggested otherwise.

Creating a Database of Georeferenced *Pv*PR Data

As with *P. falciparum*, the most globally ubiquitous and consistently *vivax* endemicity is the parasite rate (*Pv*PR), defined as the proportio sampled individuals in a surveyed population with patent parasiten blood as detected *via*, generally, microscopy or rapid diagnostic tes can provide lower sensitivity and specificity than conventional bloo and neither technique provides accuracy comparable to molecular polymerase chain reaction, PCR), the inclusion of both microscopica parasite rate data was considered important to maximise data avai across the endemic world.

To map endemicity within the boundaries of stable transmission, we exhaustive search and assembly of georeferenced *Pv*PR survey da informal literature sources and direct communications with data ge [46]. Full details of the data search strategy, abstraction and inclusi geopositioning and fidelity checking procedure are included in Pro database, completed on 25th November 2011, consisted of 9,970 q spatiotemporally unique data points, spanning the period 1985–20 spatial distribution of these data and further summaries by survey source, time period, age group, sample size, and type of diagnostic Protocol S2.

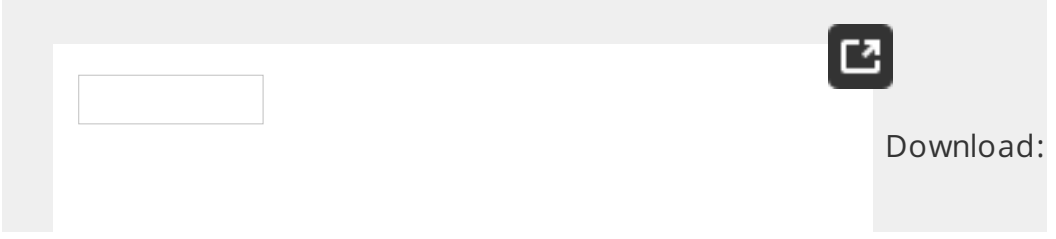

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Figure 2. The spatial distribution of *Plasmodium vivax* malaria e
Panel A shows the 2010 spatial limits of *P. vivax* malaria risk defin
further medical intelligence, temperature and aridity masks. Are
stable (dark grey areas, where *Pv*API □0.1 per 1,000 pa), unstab
areas, where *Pv*API <0.1 per 1,000 pa) or no risk (light grey, whe
1,000 pa). The community surveys of *P. vivax* prevalence conduc
January 1985 and June 2010 are plotted. The survey data are pr
continuum of light green to red (see map legend), with zero-valu
in white. Panel B shows the MBG point estimates of the annual m
2010 within the spatial limits of stable *P. vivax* malaria transmissi
same colour scale. Areas within the stable limits in (A) that were
certainty (>0.9) to have a *Pv*PR_{1-99} less than 1% were classed a
which Duffy negativity gene frequency is predicted to exceed 9
in hatching for additional context.
https://doi.org/10.1371/journal.pntd.0001814.g002

Modelling *Plasmodium vivax* Endemicity within Region Transmission

We adopt model-based geostatistics (MBG) [47], [48] as a robust an
framework for generating continuous surfaces of malaria endemici
retrospectively assembled parasite rate survey data [28], [29], [49].
special class of generalised linear mixed models, with endemicity v
pixel predicted as a function of a geographically-varying mean and
proximal data points. The mean can be defined as a multivariate fu
environmental correlates of disease risk. A covariance function is u
the spatial or space-time heterogeneity in the observed data, which
define appropriate weights assigned to each data point when pred
This framework allows the uncertainty in predicted endemicity valu
pixels, depending on the observed variation, density and sample si
different locations and the predictive utility of the covariate suite. P
survey data are dense, recent, and relatively homogenous will be p
uncertainty, whilst regions with sparse or mainly old surveys, or wh
rates are extremely variable, will have greater uncertainty. When M
using Bayesian inference and a Markov chain Monte Carlo (MCMC)
in the final predictions as well as all model parameters can be repre
predictive posterior distributions [50].

We developed for this study a modified version of the MBG framew
model *P. falciparum* endemicity [28], [29], with some core aspects of
remaining unchanged and others altered to capture unique aspect
and epidemiology. The model is presented in full in Protocol S3. As i
[49], we adopt a space-time approach to allow surveys from a wide

predictions of contemporary risk. This includes the use of a spatiote
function which is parameterised to downweight older data appropr
seasonal component in the covariance function, although we note
transmission is often only weakly represented in *Pv*PR in part becau
effect of relapses occurring outside peak transmission seasons [5
covariates were included to inform prediction of the mean function,
expectations of the major environmental factors modulating endem
indicator variable defining areas as urban or rural based on the Gl
Mapping Project (GRUMP) urban extent product [52], [53]; (ii) a long-
vegetation index product as an indicator of overall moisture availab
oviposition and survival [54], [55]; and (iii) a *P. vivax* specific index of
suitability derived from the same model used to delineate suitable a
vector survival and sporogony [45].

Age Standardisation

Our assembly of *Pv*PR surveys was collected across a variety of age
vivax infection status can vary systematically in different age group
community, it was necessary to standardise for this source of varia
surveys to be used in the same model. We adopted the same mode
described [56] and used previously for *P. falciparum* [28], [29], where
infection prevalence is expected to rise rapidly in early infancy and
childhood before declining in early adolescence and adulthood. Th
magnitude of these age profile features are likely distinct between
different endemic settings [51], [57], and so the model was parame
assembly of 67 finely age-stratified *Pv*PR surveys (Protocol S2), with
in a Bayesian model using MCMC. The parameterised model was th
observed survey prevalences to a standardised age-independent
modelling, and then further allowed the output prevalence predictio
any arbitrary age range. We chose to generate maps of all-age infe
defined as individuals of age one to 99 years (thus $PvPR_{1-99}$). We e
those less than one year of age from the standardisation because
effect of maternal antibodies, and because parasite rate surveys v
young infants. We deviated from the two-to-ten age range used for
[28], [29] because the relatively lower prevalences has meant that s
commonly carried out across all age ranges.

Incorporating Duffy Negativity

Since Duffy negative individuals are largely refractory to *P. vivax* infe
population frequencies of this phenotype have a dramatic suppres
endemicity, even where conditions are otherwise well suited for tra
predominance of Duffy negativity in Africa has led to a historical pe
absent from much of the continent, and a dearth of surveys or routi
for the parasite have served to entrench this mantra [59]. However
autochthonous *P. vivax* transmission across the continent [26], and
preclude any areas at risk *a priori*. Instead, we used a recent map o

negativity phenotypic frequency [43] and incorporated the potentia
blood group directly in the MBG modelling framework. The mapped
population fraction at each location was excluded from the denomi
data, such that any *P. vivax* positive individuals were considered to l
Duffy positive population subset. Thus in a location with 90% Duffy
individuals in a survey of 100 would give an assumed prevalence o
positives. Correspondingly, prediction of *Pv*PR was then restricted t
proportion at each pixel, with the final prevalence estimate re-conv
total population. This approach has two key advantages. First, pred
location could never exceed the Duffy positive proportion, therefor
consistency between the *P. vivax* and Duffy negativity maps. Secon
data were sparse across much of Africa, the predictions could effe
from the Duffy negativity map because predictions of *Pv*PR were re
narrower range of possible values.

Model Implementation and Map Generation

The *P. vivax* endemic world was divided into four contiguous regions
biogeographical, entomological and epidemiological characteristic
Africa formed separate regions, whilst Asia was subdivided into Ce
sub-regions with a boundary at the Thailand-Malaysia border (see
regionalisation was implemented in part to retain computational fea
number of data points, but also to allow model parameterisations t
capture regional endemicity characteristics. Within each region, a s
was fitted using a bespoke MCMC algorithm [60] to generate predic
every 5×5 km pixel within the limits of stable transmission. The pred
2010 and model outputs represent an annualised average across
year. Model output consisted of a predicted posterior distribution o
pixel. A continuous endemicity map was generated using the mean
distribution as a point estimate. The uncertainty associated with pre
summarised by maps showing the ratio of the posterior distribution
(IQR) to its mean. The IQR is a simple measure of the precision with
was predicted, and standardisation by the mean produced an unce
affected by underlying prevalence levels and more illustrative of re
performance driven by data densities in different locations. This ind
weighted by the underlying population density to produce a secon
those areas where uncertainty is likely to be most operationally imp

Refining Limits Definition and Population at Risk Estim

In some regions within the estimated limits of stable transmission, *P*
to be extremely low, either because of a dense abundance of surve
infections or, in Africa, because of very high coincident Duffy negat
frequencies. Such areas are not appropriately described as being
transmission and so we defined a decision rule whereby pixels pre
certainty (probability >0.9) of being less than 1% *Pv*PR_{1-99} were ass
class, thereby modifying the original transmission limits. These aug

were combined with a 2010 population surface derived from the GR
[53] to estimate the number of people living at unstable or stable ris
and region. The fraction of the population estimated to be Duffy neg
pixel was considered at no risk and therefore excluded from these

Model Validation

A model validation procedure was implemented whereby 10% of th
model region were selected using a spatially declustered random s
These subsets were held out and the model re-fitted in full using th
Model predictions were then compared to the hold-out data points
different aspects of model performance were assessed using valid
described previously [28], [29]. The validation procedure is detailed

Results

Model Validation

Full validation results are presented in Protocol S4. In brief, examina
in the generation of the *P. vivax* malaria endemicity point-estimate s
minimal overall bias in predicted *Pv*PR with a global mean error of −0
Africa 0.03, Central Asia −0.43, South East Asia −0.43), with values in
percentage scale (see Protocol S4). The global value thus represen
to underestimate prevalence by just under half of one percent. The
which measures the average magnitude of prediction errors, was 2
Africa 0.53, Central Asia 1.52, South East Asia 3.37), again in units of

Global *Plasmodium vivax* Endemicity and Populations

The limits of stable and unstable *P. vivax* transmission, as defined us
exclusion masks and medical intelligence data are shown in Figure
surface of *P. vivax* endemicity predicted within those limits is shown
uncertainty map (posterior IQR:mean ratio) is shown in Figure 3A an
weighted version in Figure 3B.

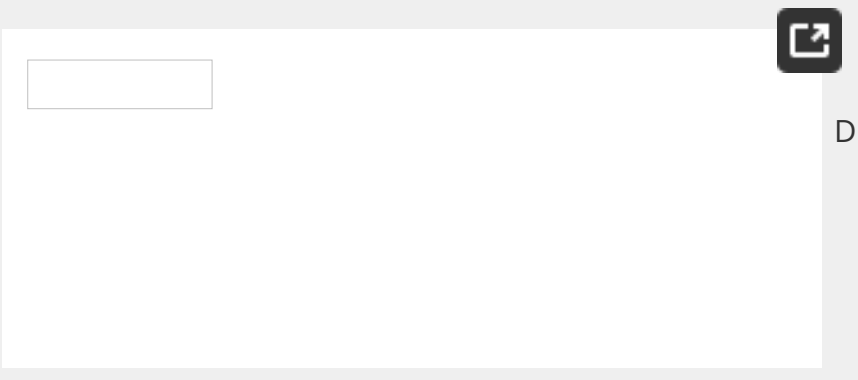

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Figure 3. Uncertainty associated with predictions of *Plasmodium*
Panel A shows the ratio of the posterior inter-quartile range to th

prediction at each pixel. Large values indicate greater uncertain
predicts a relatively wide range of *Pv*PR$_{1-99}$ as being equally pla
surrounding data. Conversely, smaller values indicate a tighter r
have been predicted and, thus, a higher degree of certainty in th
B shows the same index multiplied by the underlying population
rescaled to 0–1 to correspond to Panel A. Higher values indicate
uncertainty and large populations.
https://doi.org/10.1371/journal.pntd.0001814.g003

We estimate that *P. vivax* was endemic across some 44 million squa
approximately a third of the Earth's land surface. Around half of this
Africa (51%) and a quarter each in the Americas (22%) and Asia (27%
the uneven distribution of global populations, coupled with the prot
Duffy negativity in Africa, meant that the distribution of populations
different. An estimated 2.48 billion people lived at any risk of *P. vivax*
which a large majority lived in Central Asia (82%) with much smaller
Asia (9%), the Americas (6%), and Africa (3%). Of these, 1.52 billion li
unstable transmission where risk is very low and case incidence is
per 10,000 per annum. The remaining 964 million people at risk live
transmission, representing a wide diversity of endemic levels. The g
populations in each risk class was similar to the total at risk, such th
in both classes lived in Central Asia (Table 1).

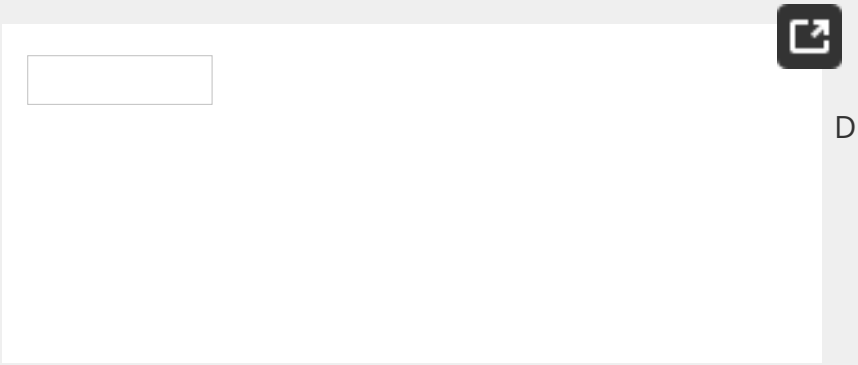

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Table 1. Area and populations at risk of *Plasmodium vivax* mala
https://doi.org/10.1371/journal.pntd.0001814.t001

Plasmodium vivax Endemicity in the Americas

Areas endemic for *P. vivax* in the Americas extended to some 9.5 mil
of which the largest proportion was in the Amazonian region of Bra
Interestingly, only a relatively small fraction of these areas (15%) ex
rather than stable transmission, suggesting a polarisation between
and those where the disease is absent altogether (Table 1). The reg
endemicity were found in Amazonia and in Central America – prima
Honduras – with predicted mean *Pv*PR$_{1-99}$ exceeding 7% in all three
important feature of *P. vivax* throughout the Americas is that its distr
approximately inverse to that of the population. This is particularly t

populous endemic countries of the region, Brazil and Mexico, and it
Americas contributed 53% of the land area experiencing stable tran
they housed only 5% of the global population at that level of risk.

Uncertainty in predicted *Pv*PR$_{1-99}$ was relatively high throughout m
(Figure 3B). This reflects the heterogeneous landscape of endemici
generally scarce availability of parasite rate surveys in the region (
However, when this uncertainty is weighted by the underlying popu
3B), its significance on a global scale is placed in context: because
risk are sparsely populated, the population-weighted uncertainty w
to parts of Africa and much of Asia.

Plasmodium vivax Endemicity in Africa, Yemen and Sau

Our decision to assume stable transmission of *P. vivax* in Africa unle
biological mask data confirmed otherwise meant that much of the c
Sahara was initially classified as being at stable risk (Figure 2A). Ho
implementing the MBG predictions of *Pv*PR$_{1-99}$ throughout this rang
posteriori those areas likely to fall below an endemicity threshold of
majority of stable risk areas were downgraded to unstable (Figure 2
maps, 92% of endemic Africa was at unstable risk, with the majority
Ethiopia, and parts of South Sudan and Somalia making up most of
stable risk. Even in these areas, endemicity was uniformly low, with
values rarely exceeding a point estimate of 2% *Pv*PR$_{1-99}$. We augm
with an additional overlay mask delineating areas where Duffy neg
prevalence has been predicted to exceed 90% (Figure 2B). The influ
group on the estimated populations at risk is profound: of the 840 m
areas within which transmission is predicted to occur, only 86 millio
risk, contributing just 3% to the global total (Table 1).

Uncertainty in predicted *Pv*PR$_{1-99}$ followed a similar pattern to the m
predictions themselves (Figure 3B). Certainty around the very low p
values covering most of the continent was extremely high – reflecti
precision gained by incorporating the Duffy negativity information t
the paucity of *P. vivax* parasite rate surveys on the continent. The po
endemicity in Madagascar and northern East Africa were predicted
In the population-weighted uncertainty map (Figure 3B), the lower p
Madagascar reduced the index on that island whereas the densely
highlands remained high.

Plasmodium vivax Endemicity in Central and South Eas

Large swathes of high endemicity, very large population densities a
presence of Duffy negativity combine to make the central and sout
Asia by far the most globally significant for *P. vivax*. We estimate tha
contributed nearly half (46%) of the global population at risk, and tw
at stable risk. China is another major contributor with 19% of the glo
primarily in unstable transmission regions, whilst Indonesia and Pa

contributed a further 12%. Within regions of stable transmission, en
to be extremely heterogeneous (Figure 2B). Areas where the point e
exceeded 7% were found in small pockets of India, Myanmar, Indon
Islands, with the largest such region located in Papua New Guinea.

The uncertainty map (Figure 3A) reveals how the most precise pred
associated with areas of uniformly low endemicity and abundant su
Afghanistan and parts of Sumatra and Kalimantan in Indonesia. Cor
higher or more heterogeneous endemicity, such as throughout the
were the most uncertain. The population-weighted uncertainty map
substantively, indicating how the populous areas of Indonesia, for e
relatively precisely predicted whereas India, China, and the Philippi
per-capita uncertainty.

Discussion

The status of *P.* vivax as a major public health threat affecting the w
regions is becoming increasingly well documented. The mantra of v
very rarely threatening and relatively benign disease [7], [10] has b
evidence suggesting that it can contribute a significant proportion
disease and death attributable to malaria in some settings [61]. Sor
pointed especially to very young children being a major source of r
some hospital-based studies have reported comparable mortality r
classified with severe *P. vivax* and severe *P. falciparum* [21], [24], [63
lethal threat by this parasite comes with evidence of failing chemot
the acute attack [64] and overdue acknowledgement of the practic
only available therapy against relapse [65]. As the international cor
increasingly ambitious targets to minimise malaria illness and deatl
progressively eliminate the disease from endemic areas [1]–[6], fur
of *P. vivax* becomes increasingly untenable.

Here we have presented the first systematic attempt to map the glo
vivax endemicity using a defined evidence base, transparent metho
measured uncertainty. These new maps aim to contribute to a more
appraisal of the importance of *P. vivax* in the broad context of malari
elimination policies, as well as providing a practical tool to support
national and sub-national levels.

Interpreting *P. vivax* Endemicity in 2010

In 2010, areas endemic for *P. vivax* covered a huge geographical ra
major continental zones and extending into temperate climates. In
important pockets of high endemicity are present, the majority of ar
transmission coincide with lower population densities, diminishing t
continent to global populations at risk. In Africa the protection confe
negativity to most of the population means the large swathes of the
transmission may occur contain only small populations at biologica

primarily in Asia where very large populations coincide with extensi
regions, and as a result nine out of every ten people at risk of *P. viva*
continent.

A number of important contrasts arise when comparing this map wi
iteration for *P. falciparum* [28]. Perhaps most obvious are the lower l
endemicity at which *P. vivax* tends to exist within populations experi
transmission. We used a cartographic scale between 0% and 7% to
variation in *P. vivax* endemicity, although point estimates exceeded
localised areas. For *P. falciparum* the equivalent scale spanned 0%
an approximate order-of-magnitude difference in prevalence of pa
part, this difference reflects the decision to standardise our predict
age range, and values would have been higher if we had opted for
range used for *P. falciparum*. This difference might be accentuated
acquisition of immunity to *P. vivax* than *P. falciparum* in the most high
A number of other biological and epidemiological differences betwe
also mean these lower apparent levels of endemicity must be interp
factor is the lower sensitivities of microscopy and RDT diagnoses fo
vivax infection prevalence, because infections tend to be associate
parasite densities which increase the likelihood of false negative di
of studies in both high and low endemic settings have found micros
prevalence by a factor of up to three when compared with molecula
[69]–[72]. The decreasing cost and time implications of molecular di
that these gold standard diagnostic techniques become the standa
surveys in the future. A global map of PCR-positive parasitemia rate
certainly reveal a larger underlying reservoir of infections and, pos
differences in patterns of endemicity than we are able to resolve cu
sensitive diagnostic methods.

The lower parasite loads must be interpreted in the context of impli
to clinical disease. For example, *Plasmodium vivax* is known to induc
comparatively lower parasite densities than *P. falciparum*, a feature
inflammatory responses of greater magnitude [16]. *P. vivax* is also c
falciparum in its potential to cause anaemia regardless of lower par
a combination of dyserythropoesis and repeated bouts of haemoly
hospital-based study at a site in eastern Indonesia of hypo- to meso
transmission of both species showed far lower frequencies of para
among inpatients classified as having not serious, serious, and fata
diagnosis of *P. vivax* compared to *P. falciparum* [24]. Further, the majo
describing severe and fatal illness with a diagnosis of vivax malaria
parasitemia >5,000/uL. In contrast, the World Health Organization t
illness attributable to hyperparasitemia with *P. falciparum* is >200,00
relationship between prevalence and risk of disease and transmiss
distinct from that for *P. falciparum*, and it is weighted more heavily to
risks at much lower parasite densities and levels of prevalence of n
parasitemia.

The capacity of *P. vivax* hypnozoites to induce relapsing infections h

important implications. First, because dormant liver stage infections
routine parasite rate surveys, our maps do not capture the potentia
of asymptomatic infections sequestered in each population. Eviden
this hidden reservoir may be substantially larger than previously th
latency *P. vivax* phenotypes both prevalent and geographically wide
contributing to clinical disease until activated, these dormant hypno
a vital role in sustaining transmission since they are refractory to bl
chemotherapy and interventions to reduce transmission. Hypnozoi
ability of *P. vivax* to survive in climatic conditions that cannot sustain
transmission. Second, the *P. vivax* parasite rates observed in popula
both new and relapsing infections, although the two are almost nev
This confounds the relationship between observed infection preva
transmission intensity such as force of infection or the entomologic
This, in turn, has implications for the use of transmission models se
optimise control options for *P. vivax* [2], [9], [27], [74]. The current una
diagnostic method for detecting hypnozoites [75] and our resulting
size and geographic distribution of this reservoir therefore remain
gaps limiting the feasibility of regional elimination [9]. It is also worth
conventional parasite rate data do not measure multiplicity of infec
additional potential confounding effect between observed infection
transmission intensity.

P. vivax in Africa and Duffy Polymorphism

Our map of *P. vivax* endemicity and estimates of populations at risk i
influenced by a single assumption: that the fraction of the populatio
negative for the Duffy antigen [43] is refractory to infection with *P. v*
empirical evidence is growing, however that *P. vivax* can infect and
negative individuals, as reported in Madagascar [76] and mainland
[77]–[80] as well as outside Africa [81], [82]. Whether the invasion o
antigen-independent pathways is a newly evolved mechanism, or w
has been overlooked by the misdiagnosis of *P. vivax* in Africa as *P. o*
unresolved [9], [42], [59]. Whilst this accumulated evidence stands
simplifying assumption of complete protection in Duffy negative ind
currently no evidence to suggest that such infections are anything
unlikely to have any substantive influence on the epidemiology or i
P. vivax at the population scale throughout most of Africa. We also m
our model for a protective effect in Duffy-negative heterozygotes, a
protection has been observed in some settings [83]–[86]. The move
within Africa of human populations from diverse ethnographic back
contemporary patterns of Duffy negativity and, in principle, could yi
with substantially reduced protection from *P. vivax* infection in the fu
implications for our map of population movement go beyond the eff
the carriage of parasites from high to low endemic regions, for exa
workers, may play an important role in sustaining transmission in s
further research is required to investigate such processes.

Mapping to Guide Control

There exists for *P. falciparum* a history of control strategies linked ex
strata of endemicity, starting with the first Global Malaria Eradicatio
[88] and undergoing a series of refinements that now feature in co
and elimination efforts. Most recently, stratification has been suppo
gained from mathematical models linking endemic levels to optimu
control options, and timelines for elimination planning [2], [89]–[95].
control options for *P. vivax* are rarely differentiated by endemicity, a
consensus around how this may be done. In part, the absence of a
strata of *P. vivax* endemicity stems from the biological complexities a
that prevent direct interpretation of infection prevalence as a metri
is also to some extent inevitable that the dogma of unstratified con
propagating: risk maps are not created because control is not diffe
endemicity, but that differentiation cannot proceed without reliable

As well as providing a basis for stratified control and treatment, the
presented here have a number of potential applications in combina
maps. First, there is an urgent need to better identify regions where
endemicity is coincident with significant population prevalence of g
dehydrogenase deficiency (G6PDd). This inherited blood disorder p
chemotherapy policy for *P. vivax* because primaquine, the only regis
against the hypnozoite liver stage is contra-indicated in G6PDd ind
cause severe and potentially fatal haemolytic reactions [96], [97]. A
G6PDd prevalence is now available (Howes et al, submitted) which
the endemicity maps presented here to provide a rational basis for
outcomes and setting appropriate testing and treatment protocols.
most clinical infections are managed without differentiating the cau
species: combining the endemicity maps for *P. vivax* and *P. falciparu*
unified strategies for malaria control programs and policy [28]. It ha
example, that artemesinin-based combination therapy (ACT) be ado
presumptively diagnosed malaria in areas coendemic for both spec
separate ACT/chloroquine treatment strategy [98]. Further, in some
50% of patients diagnosed with falciparum malaria go on to experie
malaria in the absence of risk of reinfection [99]. This high prevalen
also justify presumptive therapy with primaquine against relapse w
malaria where the two species occur at relatively high frequencies.
specific cross-parasite treatment considerations hinge on robust ri
species.

Future Challenges in *P. vivax* Cartography

Numerous research and operational challenges remain unaddress
vital insights into the geographical distribution of *P. vivax* and its imp
Perhaps the highest priority is to improve understanding of the link
prevalence and clinical burden in both *P. vivax* mono-endemic settin
coendemic with *P. falciparum*. Official estimates of national and regi

for *P. vivax* remain reliant on routine case reporting of unknown fide
crudely distinguished from *P. falciparum* [100]. It is illuminating that c
endemic countries were able to provide vivax-specific routine case
there is a clear mandate for strengthening the routine diagnosis ar
cases. Cartographic approaches to estimating *P. vivax* burden can t
role in triangulating with these estimates to provide insight into the
disease independent of health system surveillance and its attenda
[101]–[105]. There is also a particular need to define burden and cl
associated with *P. vivax* in pregnancy [9], [106] and other clinically v
most notably young children. Linking infection prevalence to clinica
need to better understand the contribution of relapsing infections t
magnitude of this contribution is known to be highly heterogeneous
pattern is poorly measured and causal factors only partially unders

Further challenges lie in understanding how *P. falciparum* and *P. viva*
human hosts and how these interactions manifest at population lev
maps for each species reveals a complete spectrum from areas en
parasite through to others where both species are present at broa
identifying these patterns of coendemicity is an important first step
terms of risks of coinfection and clinical outcomes, antagonistic me
elevated severe disease risk, or cross-protective mechanisms of ac
remain disputed [20], [107]–[109].

Conclusions

To meet international targets for reduced malaria illness and death
cause of regional elimination, the malaria research and control com
longer afford to neglect the impact of *P. vivax*. Its unique biology and
present challenges to its elimination that greatly surpass those of it
cousin, *P. falciparum*. Making serious gains against the disease will
strengthening of the evidence base on almost every aspect of its b
control and treatment. The maps presented here are intended to co
They are all made freely available from the MAP website [110] along
individual maps for every malaria-endemic country. Users can acce
images or download the global surfaces for use in a geographical i
allowing them to integrate this work within their own analyses or pr
overlays and displays. We will also make available, where permissi
obtained, all underlying *P. vivax* parasite rate surveys used in this w

Supporting Information

Protocol S1.

Updating the global spatial limits of *Plasmodium vivax* malaria tra
S1.1 Overview. S1.2 Identifying Countries Considered *P. vivax* Malari
Updating National Risk Extents with *P. vivax* Annual Parasite Incidenc

Masks of Transmission Exclusion. S1.5 Risk Modulation Based on M
S1.6 Assembling the *P. vivax* Spatial Limits Map. S1.7 Refining Regior
Transmission after MBG Modelling. S1.8 Predicting Populations at R
https://doi.org/10.1371/journal.pntd.0001814.s001
(DOC)

Protocol S2.

The Malaria Atlas Project *Plasmodium vivax* parasite prevalence da
Assembling the *Pv*PR Data. S2.2 Database Fidelity Checks. S2.3 Data
*Pv*PR Input Data Set. S2.5 Age-Standardisation. S2.6 Regionalisation
https://doi.org/10.1371/journal.pntd.0001814.s002
(DOC)

Protocol S3.

Bayesian model-based geostatistical framework for predicting *Pv*P
Inference. S3.2 Model Overview. S3.3 Formal Presentation of Model.
https://doi.org/10.1371/journal.pntd.0001814.s003
(DOC)

Protocol S4.

Model validation procedures and additional results. S4.1 Creation
Procedures for Testing Model Performance. S4.3 Validation Results
https://doi.org/10.1371/journal.pntd.0001814.s004
(DOC)

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Author Contributions

Conceived and designed the experiments: PWG SIH. Performed the
APP DLS. Analyzed the data: PWG APP DLS IRFE CAG KEB. Contribute
reagents/materials/analysis tools: IRFE CLM CAG MFM KEB APP AJT R
IM JKB. Wrote the paper: PWG.

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