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CHAPTER ONE

The Global Public Health Significance of *Plasmodium vivax*

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Abstract

Plasmodium vivax occurs globally and thrives in both temperate and tropical climates. Here, we review the evidence of the biological limits of its contemporary distribution and the global population at risk (PAR) of the disease within endemic countries. We also review the most recent evidence for the endemic level of transmission within its range and discuss the implications for burden of disease assessments. Finally, the evidence-base for defining the contemporary distribution and PAR of *P. vivax* are discussed alongside a description of the vectors of human malaria within the limits of risk. This information along with recent data documenting the severe morbid and fatal consequences of *P. vivax* infection indicates that the public health significance of *P. vivax* is likely to have been seriously underestimated.

1. INTRODUCTION

Malaria is a highly significant global public health problem. Its greatest burden is imposed on the world's poorest countries (Sachs and Malaney, 2002). It is the third leading cause of death from infectious diseases for children under age of five worldwide (Black et al., 2010) and the fourth leading cause for all ages (WHO, 2008). After decades of neglect, malaria control research and financing has experienced a resurgence in recent years (RBMP, 2008) and targets have been raised by international initiatives aiming for the goal of elimination (Feachem et al., 2009; Chitnis et al., 2010a; Moonen et al., 2010; Tanner and Hommel, 2010; Tatem et al., 2010; Alonso et al., 2011). While elimination goals ostensibly address all human malarias, the allocation of funding and resources between the two parasites of greatest significance, *Plasmodium falciparum* and *Plasmodium vivax*, has been highly disparate. From 2007 to 2009, only 3.1% of all malaria research and development funding was targeted at *P. vivax* (PATH, 2011). *Plasmodium vivax* is epidemiologically and biologically different to *P. falciparum* and it is not, therefore, possible to assume that control methods developed for falciparum malaria are transferable to vivax malaria (Luxemburger et al., 1994; Bockarie and Dagoro, 2006; Baird, 2010; Bousema and Drakeley, 2011). Evidence from *P. vivax* infections in carefully monitored populations show that vivax malaria should no longer be thought of as a benign and rarely fatal disease but one that can lead to severe disease and death (Baird, 2007; Price et al., 2007b; Anstey et al., 2009). The reader is referred to an accompanying review in this thematic volume of *Advances in Parasitology* (Chapter 3, Volume 80), which addresses the clinical severity of *P. vivax*. The clinical importance of *P. vivax*, along with its wide geographic distribution extending well beyond the limits of falciparum malaria (Guerra et al.,

2006a, 2006b, 2010; Gething et al., 2011b) and the challenges it presents for control (Sattabongkot et al., 2004; Wells et al., 2010), has led to a call for greater attention to be paid to understanding the global distribution and burden of this neglected parasite (Baird, 2007; Price et al., 2007b; Mueller et al., 2009a).

A key information gap impeding *P. vivax* control and progress towards elimination has been the lack of geographical estimates of risk (Mendis et al., 2001; Price et al., 2007b; Malaria Eradication Research Agenda, 2011b). Assessment of geographic variations in levels of endemicity of the parasite is essential to estimate the burden of the disease and measure the impact of control and the feasibility of elimination (Pampana, 1969; Hay et al., 2008; Tatem et al., 2010). The Malaria Atlas Project (MAP) was founded to address this evidence gap (Hay and Snow, 2006; Hay et al., 2009; Gething et al., 2011a), with an initial focus on *P. falciparum*, and the resulting global malaria distributions have been used to assess the adequacy and equity in control funding (Pigott et al., 2012), to inform international policy and resource allocation (Anonymous, 2009; Feachem et al., 2009; McLaughlin et al., 2009; World Bank, 2009; Zanzibar Malaria Control Program, 2009; DFID, 2010; Global Partnership to Roll Back Malaria et al., 2010) and to estimate the global burden of disease (Patil et al., 2009; Gething et al., 2010a; Hay et al., 2010b). A suite of modelled spatial data on *P. vivax* transmission and endemicity (Guerra et al. 2010; Gething et al. 2012) and *P. vivax* vectors (Sinka et al., 2010a, 2010b, 2011, 2012) add to this evidence base for strategic disease-control planning, implementation and monitoring. Here, for the first time, we bring all these mapped data on *P. vivax* together in one place. We explain how these products were generated, their limitations and their value, and provide an overview for each malaria-endemic region of the world. We also consider those areas where our lack of geographical knowledge is particularly acute and would benefit most from concerted future research efforts. A full review of the methodologies used to generate each mapped product is also provided at the end of this chapter.

2. THE GLOBAL DISTRIBUTION OF *P. VIVAX* INFECTIONS

Plasmodium vivax has the widest geographical distribution of the human malarias with an estimated 2.49 billion individuals living at risk of infection in 2010 (Gething et al., 2012). Biological features of *P. vivax* that distinguish it from *P. falciparum* present unique challenges to the control of

the parasite (Mendis et al., 2001; Sattabongkot et al., 2004; Wells et al., 2010); in elimination settings, *P. vivax* is often the 'last parasite standing' (Garnham, 1951; Yekutiel, 1960; Pampana, 1969; Wernsdorfer et al., 2009; Tatem et al., 2010). *Plasmodium vivax* gametocytes are present earlier in the progression of a primary or recrudescent infection than *P. falciparum* (Mendis et al., 2001; McKenzie et al., 2002), such that the majority of patients have sufficient gametocytaemia to allow transmission before the infection is diagnosed or treated (Ratcliff et al., 2007; Awab et al., 2010; Douglas et al., 2010). *Plasmodium vivax* gametocytes are transmitted more efficiently to *Anopheles* mosquito vectors (Boyd and Kitchen, 1937; Collins et al., 2002) than those of *P. falciparum* and are transmissible at lower parasite densities (Sattabongkot et al., 2004). Within the mosquito, vivax sporozoites develop faster than *P. falciparum* and with slightly wider viable temperature ranges, allowing for a greater geographical distribution (Gething et al., 2011b). In addition, due to vector bionomics in regions where *P. vivax* is most prevalent, methods of control that are broadly effective in reducing *P. falciparum* transmission, such as insecticide-treated bed nets (ITNs), show far less success in the control of *P. vivax* (Luxemburger et al., 1994; Bockarie and Dagoro, 2006). *Plasmodium vivax* malaria is typically carried with lower levels of parasitaemia, making it relatively difficult to diagnose (Mendis et al., 2001). However, there is evidence that, despite lower blood parasite loads, *P. vivax* immunity is acquired more rapidly than *P. falciparum* and may result in an earlier age-prevalence peak in areas of high transmission (Mueller et al., 2009a, 2009b). Detailed reviews regarding the biology (Chapter 2, Volume 80), control (Chapter 6, Volume 80), and acquired immunity (Chapter 3, Volume 81) of *P. vivax* are available elsewhere in this thematic issue of *Advances in Parasitology*.

Perhaps the most important feature of *P. vivax* biology is its ability to relapse in the weeks and months following a primary parasitaemia, via a dormant liver stage known as the hypnozoite (James, 1931; Coatney, 1976; Garnham, 1989; Prudencio et al., 2006; Chen et al., 2007; Imwong et al., 2007; White, 2011). It has long been known that there is significant geographical variation in the rate at which a 'strain' of *P. vivax* may relapse (Coatney and Cooper, 1948; Winckel, 1955; Garnham et al., 1975). The exact mechanism through which hypnozoite relapses are triggered is unknown (Cogswell, 1992; Prudencio et al., 2006; Baird, 2009; Mueller et al., 2009a). One theory is that the mechanism is an adaptive trait of the parasite to sequester or 'hibernate' during times when climatic conditions would be inhospitable to the *Anopheles* vector of the disease (Shute et al., 1976; Baird and Rieckmann, 2003; White, 2011). This theory is supported by observations that temperate strains of the parasite tend to exhibit

longer relapse intervals than tropical strains (Garnham et al., 1975; Shute et al., 1976; Cogswell, 1992; Collins and Jeffery, 1996; Adak et al., 1998; Baird et al., 2007; Imwong et al., 2007). Primaquine is currently the only widely available drug with activity on the hypnozoite stage capable of preventing relapse (Baird and Hoffman, 2004; Galappaththy et al., 2007), but is associated with haemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency (Beutler, 1994; Baird and Hoffman, 2004; Cappellini and Fiorelli, 2008). Primaquine is contraindicated in pregnant women because of the risk of haemolytic anaemia in the foetus of unknown G6PD status (WHO, 2010a). The reader is referred to reviews that address relapse (Chapter 2, Volume 80), treatment (Chapters 4 and 5, Volume 80) and G6PD deficiency (Chapter 4, Volume 81), which are provided elsewhere in this special issue *Advances in Parasitology*. Relapse also has implications for understanding the burden of *P. vivax* malaria based on prevalence rates derived from malariometric surveys and cartographic studies (Patil et al., 2009; Hay et al., 2010b).

To accurately illustrate *P. vivax* endemicity, it is necessary to incorporate the distribution of the Duffy-negative phenotype. The varying prevalence of Duffy negativity in populations throughout the world is a significant determinant of the distribution of *P. vivax* (Livingstone, 1984). Duffy-negative individuals are, for the most part, refractory to *P. vivax* infection and the phenotype is found at highest frequencies in Africa, whereas it is relatively rare elsewhere (Howes et al., 2011). A detailed review of the effect of Duffy negativity on the epidemiology of *P. vivax* (Chapter 2, Volume 81) is provided elsewhere in this series. The influence of Duffy negativity on *P. vivax* transmission reinforces the need to differentiate strategies employed to generate and interpret maps of *P. vivax* endemicity from those used for *P. falciparum* (Hay et al., 2009; Gething et al., 2011a).

Until recently, little work had been done to define the geographic limits and risk of *P. vivax* infection. The only map including vivax malaria endemicity was that of Lysenko from 1968 (Lysenko and Semashko, 1968). As shown in Fig. 1.1, Lysenko defined endemicity as the parasite rate (PR) in children aged between 2 and 10 years old (hypoendemic <10%, mesoendemic 11–50%, hyperendemic 51–75%), with the exception of the holoendemic class (>75%) where the PR was defined in the 1-year age cohort. The map was derived from a synthesis of historical records and malariometric indices of all four human malaria parasites: disease and vector presence and absence records; spleen, parasite, sporozoite and biting rates; sickle cell incidence; and others (Hay et al., 2004; Gething et al., 2010b). Lysenko interpolated the data globally to determine the distribution of
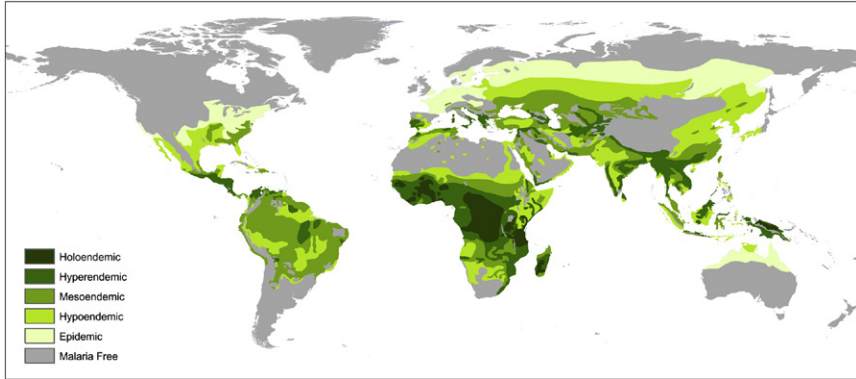
Figure 1.1 The Lysenko map of global malaria endemicity. The map was digitised from its original source (Lysenko and Semashko, 1968) where endemicity classes were defined by parasite rate (PR) in children between 2 and 10 years old (hypoendemic <10%, mesoendemic 11–50%, hyperendemic 51–75%), with the exception of the holo-endemic class (>75%) where the parasite rate was defined in the 1-year age cohort. The 'epidemic' class is restricted to the temperate regions in these maps and it should be noted that this term is used differently today. For a colour version of this figure, the reader is referred to the online version of this book.

malaria at the peak of its historic distribution (*circa* 1900) using expert opinion, temperature ranges and rainfall isohyets (Lysenko and Semashko, 1968; Lysenko and Beljaev, 1969; Kaneko et al., 1998).

Lysenko's endemicity map was not specific to one human malaria parasite. The map was created before the advent of geographic information systems (GIS) and lacks geographic precision – as exemplified by a significant misplacement of the Nile River. Relative to the remote sensing data available today, the environmental data Lysenko and Semashko used to refine the endemicity boundaries were both limited and crude. The evidence base used was not described in detail and, since the map was not generated via a formal statistical method, there was no measure of uncertainty provided. It is therefore difficult to determine how robust the distribution estimates of Lysenko were.

3. SPATIAL DISTRIBUTION OF *P. VIVAX* MALARIA, POPULATIONS AT RISK AND ITS VECTORS

Here, we bring together maps at the regional level (Fig. 1.2) of the limits of transmission, endemicity and estimates of the populations at risk, along with the distribution of *P. vivax* vectors.
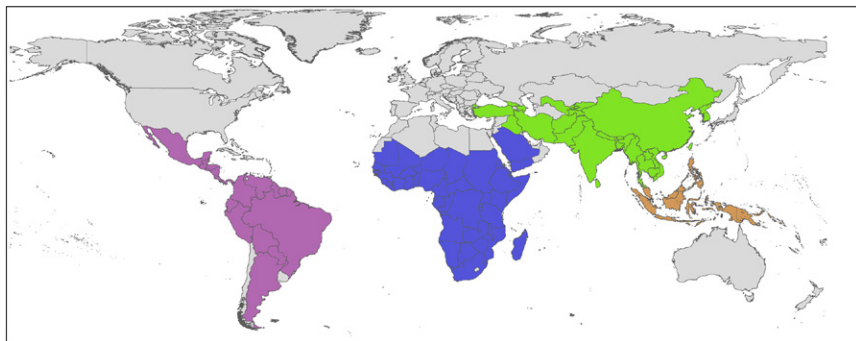
Figure 1.2 Regional tiles of *Plasmodium vivax* endemic countries. The regional tiles shown were used to stratify the modelling of *P. vivax* endemicity. Pink = the Americas; blue = Africa+; green = Asia; orange = Asia-Pacific; grey = non endemic for *P. vivax*. For interpretation of the references to colour in this figure legend, the reader is referred to the online version of this book.

3.1. *P. vivax* Malaria Limits and Endemicity

Figure 1.3 shows estimated limits of unstable (light grey) and stable (dark grey) transmission of *P. vivax* in Panel 1 (A1–D1) and, within Panel 2 (A2–D2), levels of endemicity (blue to yellow to red, red being >7% prevalence). The map is accompanied by two measures of uncertainty in our endemicity estimates: one absolute measure and the second weighted by population density in each location (Fig. 1.4).

A detailed review of the data and methodology used to create this map is given at the end of this chapter in Section 6. In brief, we have used 9970 spatiotemporally unique records of parasite prevalence (Fig. 1.3, Panel 1), environmental covariates and a Bayesian geostatistical model with seasonal and age-standardisation components to generate a smooth map of point estimates of parasite prevalence in all areas with stable transmission (Gething et al., 2012). Throughout the world, endemicity was predicted within a relatively narrow range, with the point estimate of the *P. vivax* PR age-standardised to the 1–99 year age range ($PvPR_{1-99}$) rarely exceeding 7%. Here, we highlight important aspects of the methodological approach taken that improve on preceding global estimates of *P. vivax* malaria risk, along with key assumptions and constraints:

Temporal influence. The maps presented (Figure 1.3, Panel 2) are of endemicity in 2010 but the data used to inform the model ranged from 1985 to 2010. The model was designed to down-weight older data, so that whilst they can help inform the contemporary estimates, particularly in areas lacking contemporary data, these had less influence on our estimates of prevalence. This was reflected by higher uncertainty those areas reliant on older data.
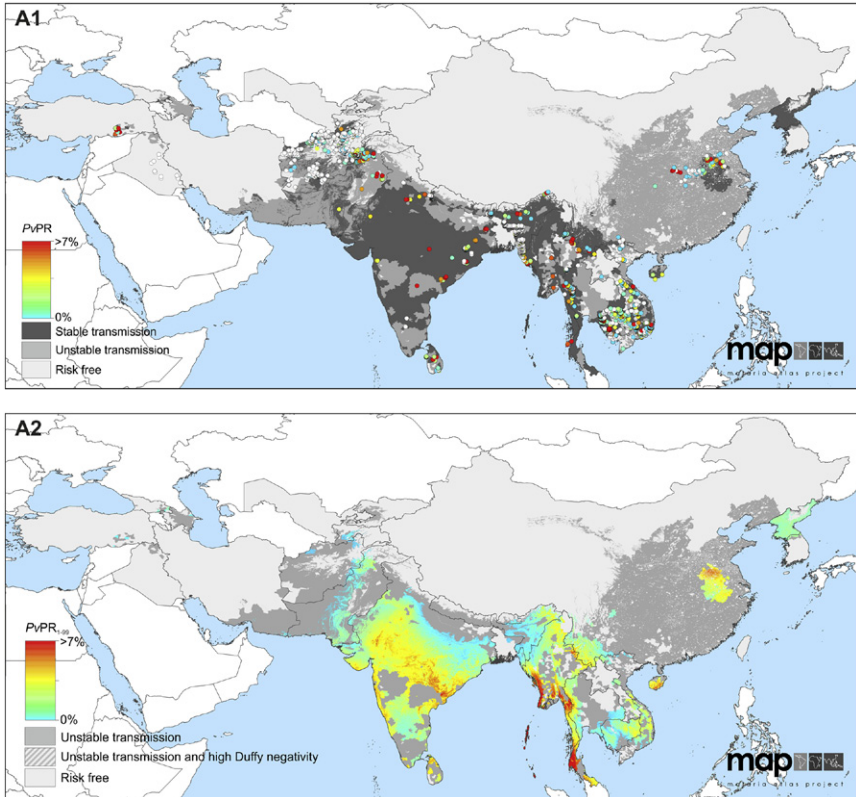
Figure 1.3 The spatial distribution of *Plasmodium vivax* malaria endemicity in 2010 in Asia, Asia-Pacific, the Americas and Africa+. The spatial distribution of *P. vivax* malaria endemicity is shown at the regional levels: Asia (A), Asia-Pacific (B), the Americas (C) and Africa+ (D). Panel 1 in A–D shows the 2010 spatial limits of *P. vivax* malaria risk defined by *Plasmodium vivax* annual parasite incidence (*Pv*API) with further medical intelligence, temperature and aridity masks. Areas were defined as stable (dark grey areas, where *Pv*API ≥ 0.1 per 1000 per annum), unstable (medium grey areas, where *Pv*API < 0.1 per 1000 p.a.) or no risk (light grey, where *Pv*API = 0 per 1000 p.a.). Only the *P. vivax* malaria endemic countries (*Pv*MECs) in each region are shaded in. The community surveys of *P. vivax* prevalence conducted between January 1985 and June 2010 are plotted. The survey data are presented as a continuum of light blue to red (see map legend), with zero-valued surveys shown in white. Panel 2 in each region shows the model-based geostatistics (MBG) point estimates of the annual mean $PvPR_{1-99}$ for 2010 within the spatial limits of stable *P. vivax* malaria transmission, displayed on the same colour scale. Areas within the stable limits (Panel 1) that were predicted with high certainty (>0.9) to have a $PvPR_{1-99}$ less than 1% were classed as unstable. Areas in which Duffy negativity gene frequency is predicted to exceed 90% (Howes et al., 2011) are shown in hatching for additional context. For interpretation of the references to colour in this figure legend, the reader is referred to the online version of this book.
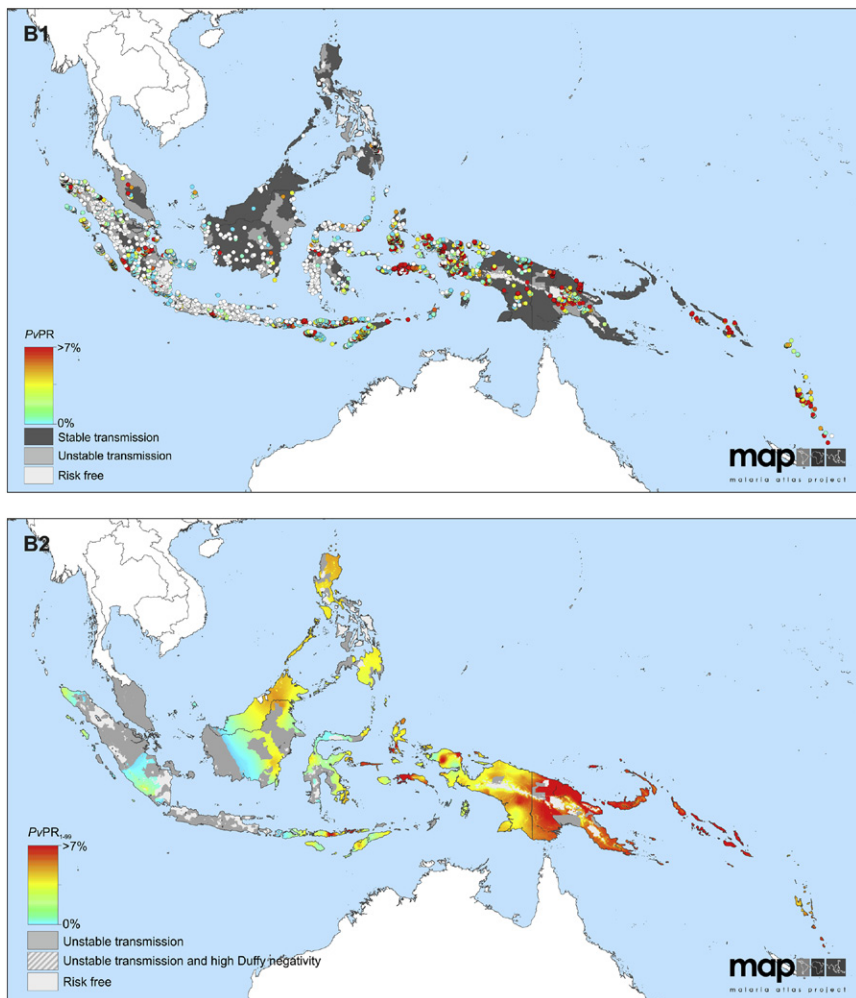
Figure 1.3, cont'd

Seasonal fluctuations. The estimates provide the average *P. vivax* endemicity over a year. Seasonal fluctuations of parasite prevalence were included in the model structure but aggregated in the outputs. Seasonal estimates are not currently available and would be confounded by relapses that can occur outside the transmission season (see the section 'Relapse of *Plasmodium vivax* blood infections' below).

Smoothness of the global map. Malaria endemicity can be highly heterogeneous over small distances and, therefore, our model produced candidate maps that are also highly heterogeneous. An artefact of presenting one map that summarises the full model output using either a mean or a median
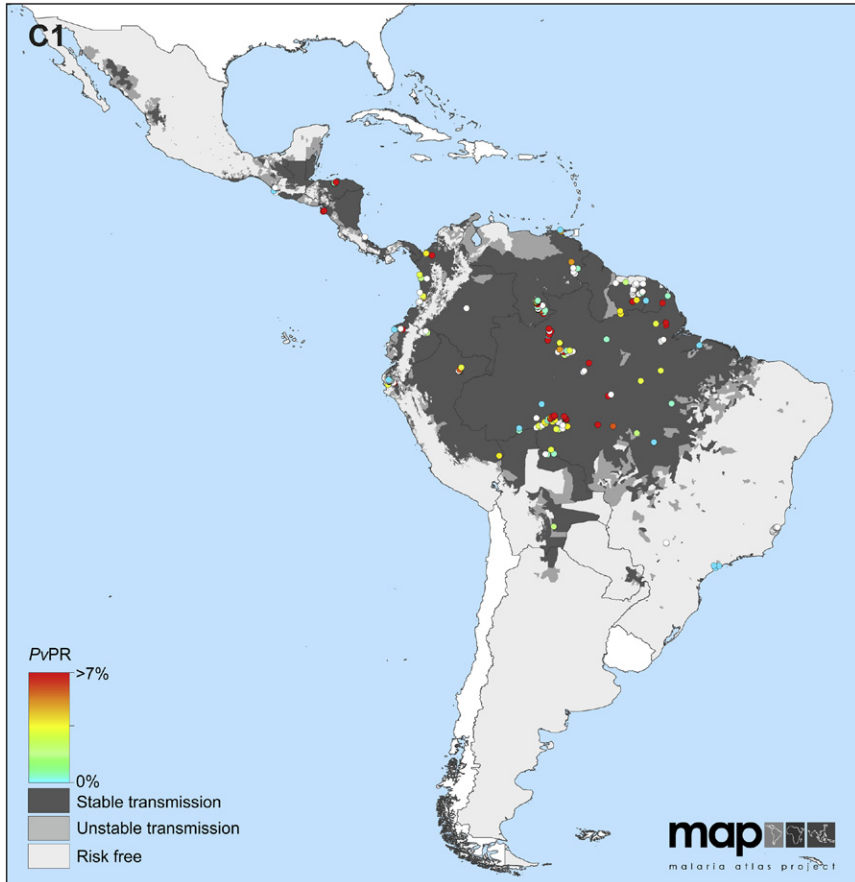
Figure 1.3, cont'd

of the estimates for each location was that this process smoothed out the patchy nature of malaria endemicity.

  Use of parasite prevalence data. It is important that our estimates were based on real data, with a mathematical model that compensated for the fact that the real data were neither comprehensive nor universally contemporary. The most commonly available metric from almost all countries is prevalence (often referred to as parasite rate (PR)), estimated from surveys that are conducted using a common methodology (Hay et al., 2008). Prevalence data are relatively robust but have the disadvantage that required sample sizes become prohibitively large when prevalence rates are low.

  Use of clinical incidence data. Annual clinical incidence per 1000 people (commonly referred to as annual parasite incidence (API) data) from public
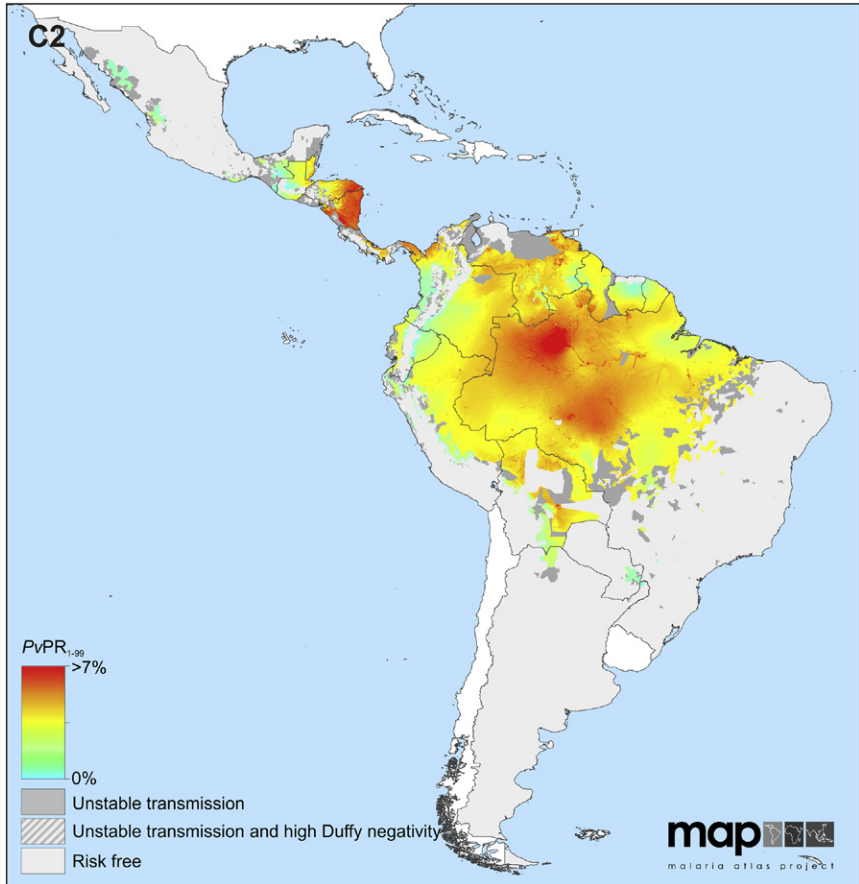
Figure 1.3, cont'd

health records is more sensitive at low parasite prevalence values, but is biased. For example, we do not know the proportion of people within every district who do not seek care for malaria at a public health facility and are therefore missed by the statistics. We used clinical incidence data to define the areas where we know very little, other than that malaria exists but is so low as to be essentially unquantifiable using available data. We referred to this level of risk as unstable malaria transmission and defined it as less than one case per 10,000 people per year (or <0.1 API). At very low levels of incidence, a small change is proportionally large so API is measured across an administrative (ADMIN) division and we averaged this figure over 4 years (providing data are available).
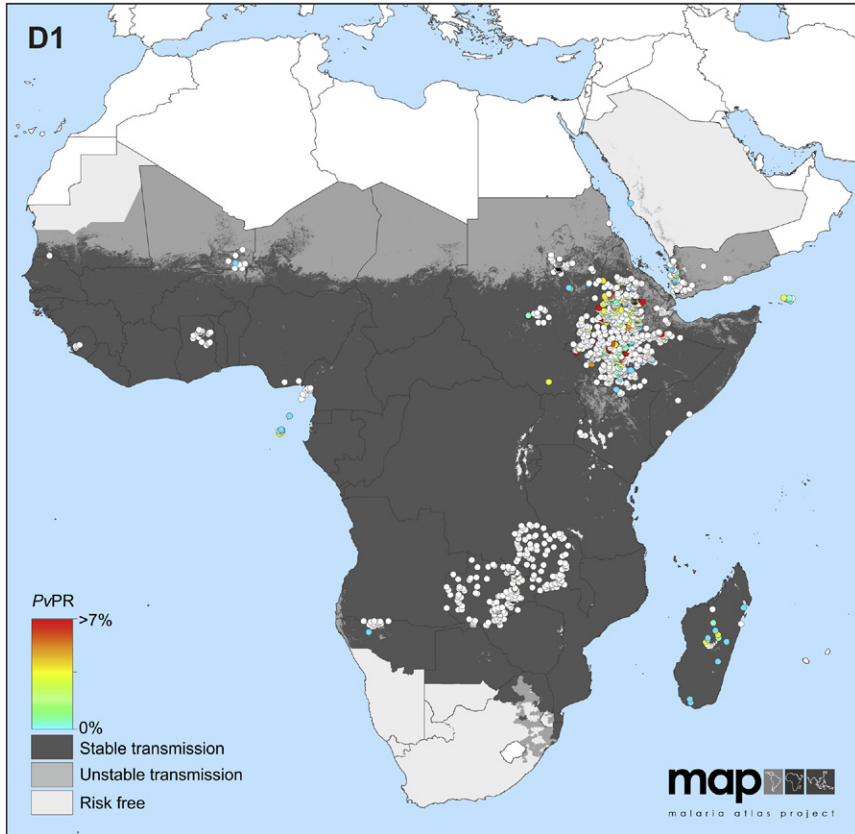
Figure 1.3, cont'd

Use of biological data to refine the limits defined by clinical incidence data. Remote sensing surfaces, showing temperature (Fig. 1.5) and aridity (Fig. 1.6), and biological models were used to identify areas where extreme temperature or aridity regimes would reduce or preclude *P. vivax* transmission. The limits of transmission are adjusted accordingly.

The effect of interventions. The PR data used came from many areas where interventions (ITNs, indoor residual spraying (IRS), etc.) have been implemented so that the effect of these interventions at these locations was included within the estimates produced by the model. This effect was not modelled separately and cannot be extracted from our results.

The impact of Duffy negativity. Since Duffy negative individuals are largely refractory to *P. vivax* infection (Miller et al., 1976), high population frequencies of this phenotype suppress endemicity, even where conditions are
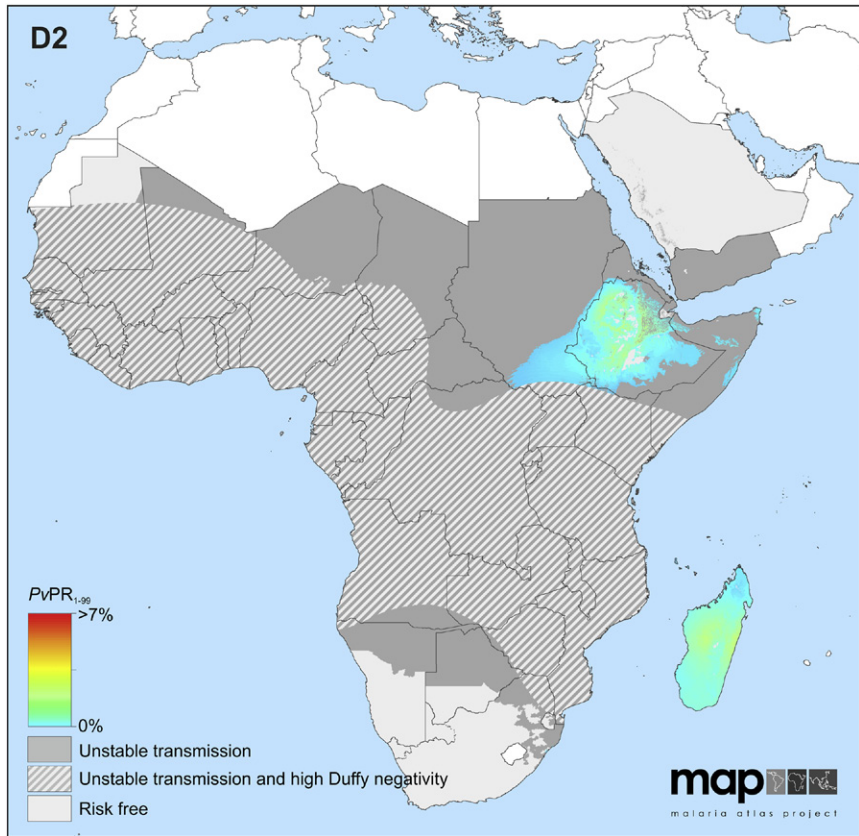
Figure 1.3, cont'd

otherwise well suited for transmission (Guerra et al., 2010). We incorporated recent global estimates of the frequencies of Duffy negativity (Howes et al., 2011) in our model. Regional maps of the predicted prevalence of Duffy negativity are shown in Fig. 1.7. The fraction of the population at each population that was Duffy-negative was excluded from the denominator in the prevalence data, such that any *P. vivax*-positive individuals are assumed to have arisen from the Duffy-positive population subset. Thus, in a location with 90% Duffy negativity, five positive individuals in a survey of 100 would give an assumed prevalence of 50% amongst Duffy positives. Correspondingly, prediction of prevalence was then restricted to the Duffy-positive proportion, with the final prevalence estimate re-converted to refer to the total population. This approach meant prevalence could never exceed the Duffy-positive proportion of a population and, where *P. vivax*
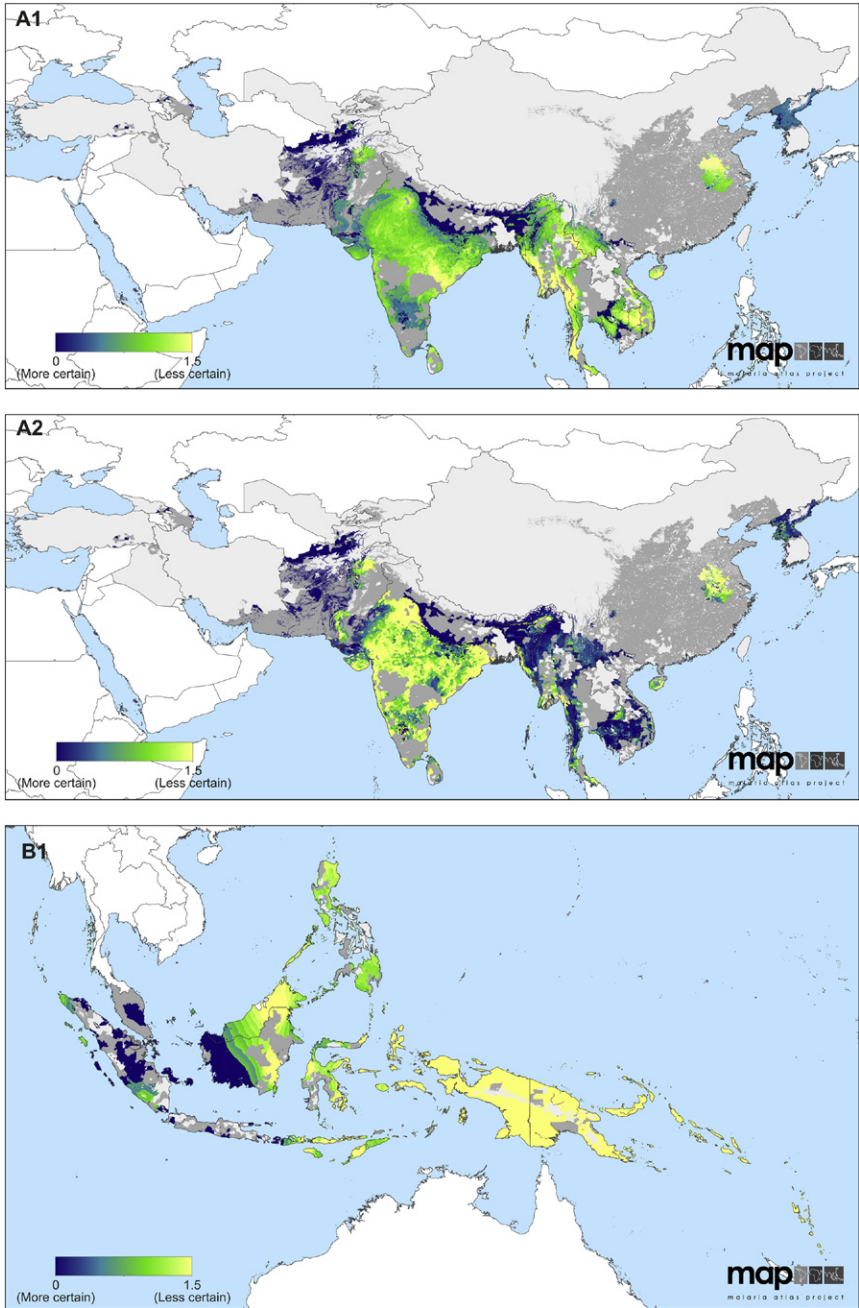
Figure 1.4 Uncertainty associated with predictions of *Plasmodium vivax* endemicity in Asia, Asia-Pacific, the Americas and Africa+.
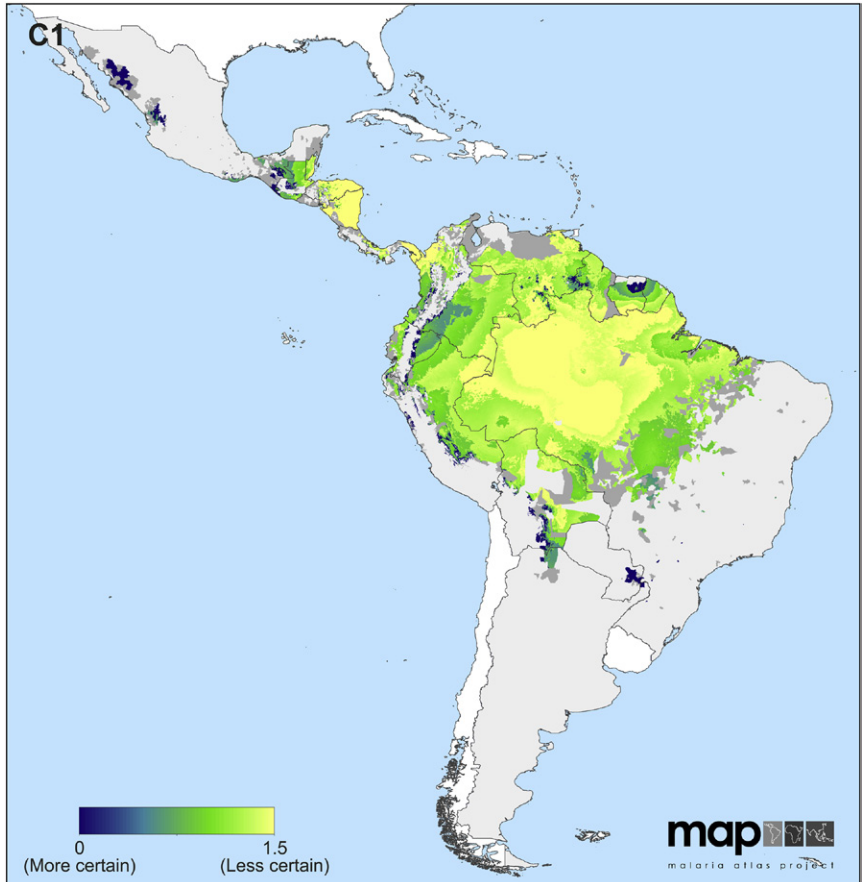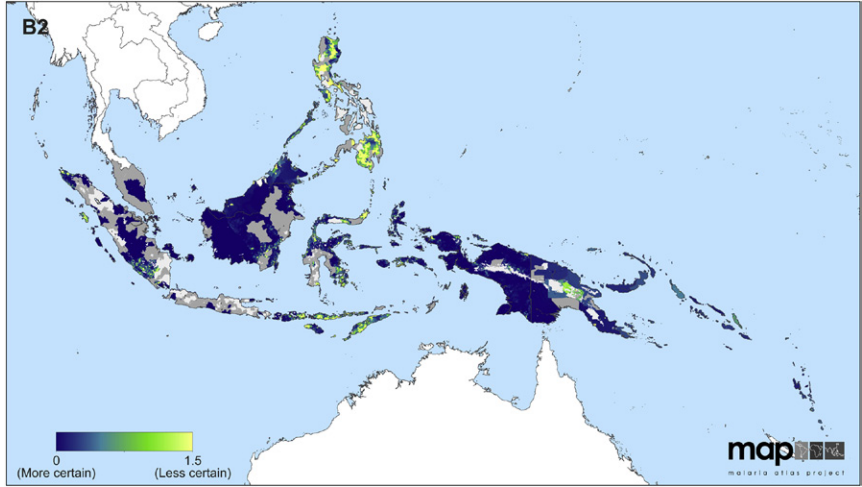
Figure 1.4, cont'd
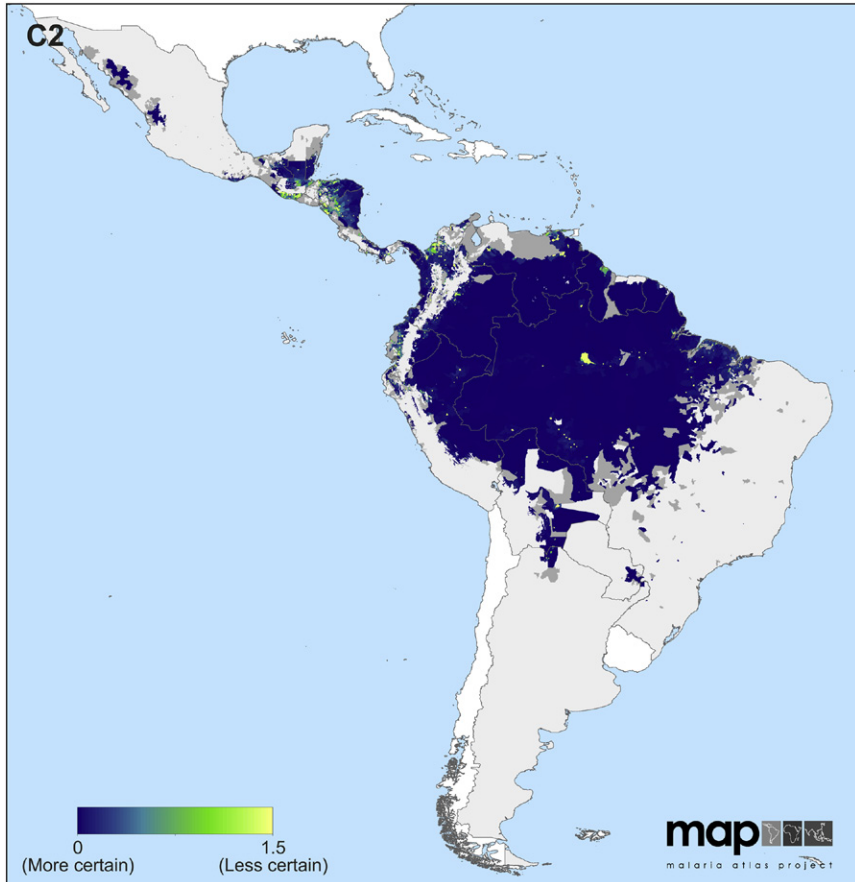
Figure 1.4, cont'd The uncertainty associated with *P. vivax* malaria endemicity predictions is shown at the regional levels: Asia (A), Asia-Pacific (B), the Americas (C) and Africa+ (D). Panel 1 in A–D shows the ratio of the posterior inter-quartile range to the posterior mean prediction at each pixel. Large values indicate greater uncertainty: the model predicts a relatively wide range of $PvPR_{1-99}$ as being equally plausible given the surrounding data. Conversely, smaller values indicate a tighter range of values have been predicted and, thus, a higher degree of certainty in the prediction. Panel 2 in each region shows the same index multiplied by the underlying population density and rescaled to 0–1 to correspond to Panel 1. Higher values indicate areas with high uncertainty and large populations. Areas of no risk within *Pv*MECs are shown in grey and countries not endemic for *P. vivax* or outside the named region are in white. For a colour version of this figure, the reader is referred to the online version of this book.

survey data were sparse across much of Africa, the prevalence predictions could borrow strength from the Duffy negativity map because predictions of prevalence were restricted to a narrower range of possible values.
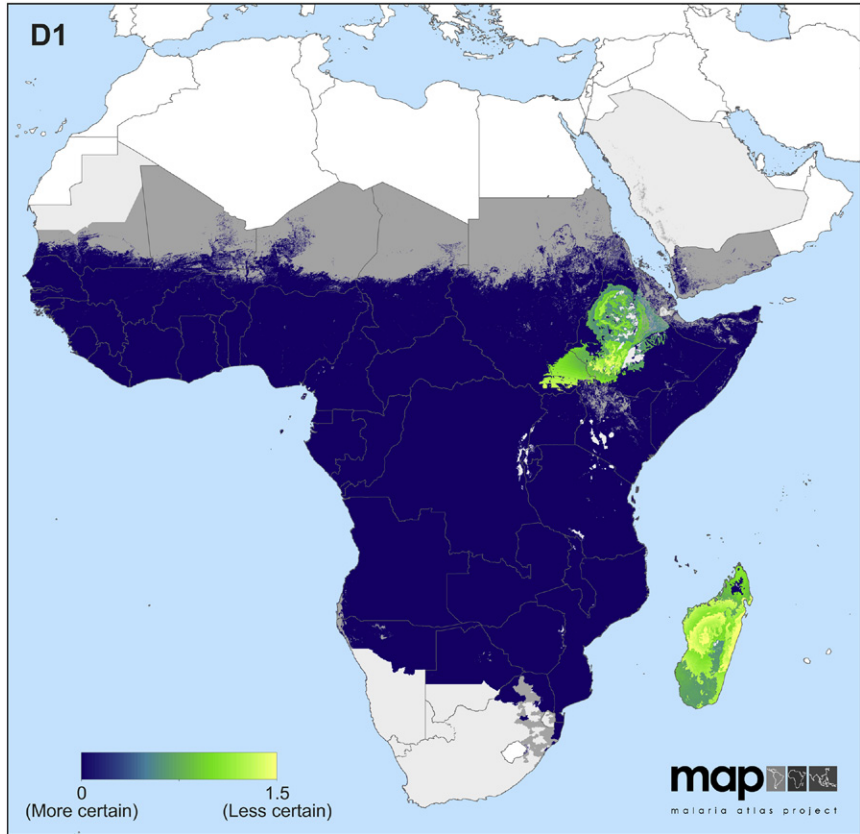
Figure 1.4, cont'd

Transmission in Africa. The predominance of Duffy negativity in Africa has led to a historical perception that *P. vivax* is absent from much of the continent (Rosenberg, 2007). Evidence exists, however, of autochthonous *P. vivax* transmission in nearly every African country (Guerra et al., 2010) and that *P. vivax* is capable of causing severe disease in the continent (Mahgoub et al., 2012). Therefore, we did not preclude any areas at risk before modelling endemicity. We initially assumed stable *P. vivax* transmission, unless the biological mask layers or clinical incidence (API) data confirmed otherwise. In some regions provisionally labelled as stable in this way, the endemicity model subsequently predicted extremely low prevalence, either because of survey data reporting zero infections or because of very high Duffy-negativity prevalence. Locations predicted with high certainty (probability >0.9) of being less than 1% prevalence were therefore re-assigned
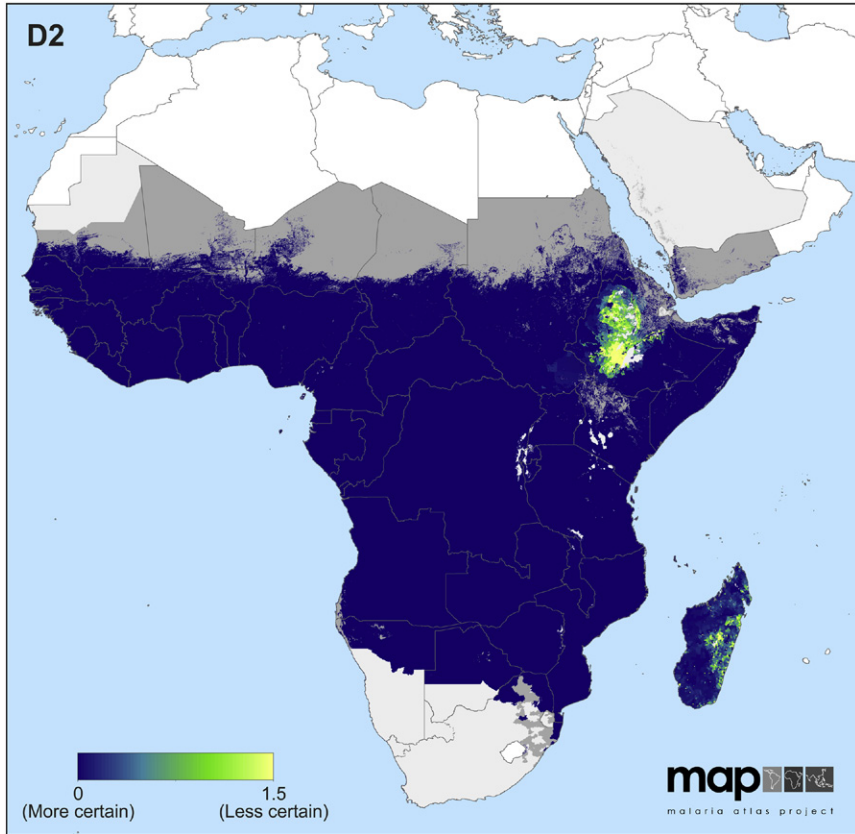
Figure 1.4, cont'd

to the unstable transmission class. This re-assignment is shown in the final limits presented in Fig. 1.3A1–D2.

Relapse of Plasmodium vivax *blood infections.* The prevalence surveys used detect parasites in the blood and not latent infections in the liver. Primary blood infections detected by these surveys are indistinguishable from relapses caused by previously dormant parasites from the liver. The estimates produced by the model were, therefore, the combined prevalence of primary infections and relapses.

The impact of low parasitaemia levels. Plasmodium vivax parasites are typically found in the blood at much lower densities than are found for *P. falciparum* and so are less likely to be detected by some diagnostic methods. We made no direct adjustments for these 'sub-patent' infections. It is important to note that *P. vivax* can cause fever and anaemia at lower

Figure 1.5 Environmental suitability for transmission of *P. vivax* as defined by temperature in Asia, Asia-Pacific, the Americas and Africa+. Areas shaded green in Asia (A), Asia-Pacific (B), the Americas (C) and Africa+ (D) are those in which no windows exist across an average year in which the annual temperature regime is likely to support the presence of infectious vectors. The temperature suitability model is described in full elsewhere (Gething et al., 2011b). For interpretation of the references to colour in this figure legend, the reader is referred to the online version of this book.

parasitaemia levels than *P. falciparum* (Mendis et al., 2001; Mueller et al., 2009a).

Uncertainty in the estimates of endemicity. The modelling framework allowed the uncertainty in predicted endemicity values to vary between locations, depending on the observed variation, density and sample size of surveys and the predictive utility of the suite of environmental covari–ates (described in detail in Section 1.6). The uncertainty associated with

Figure 1.5, cont'd

predictions is summarised by maps showing the ratio of the inter-quartile range (IQR) to its mean (Fig. 1.4A1–D1). The IQR is a simple measure of the precision with which each value is predicted, and standardisation by the mean produces an uncertainty index less affected by underlying prevalence levels and more illustrative of relative model performance. This index was then also weighted by the underlying population density to produce a second map indicative of those areas, where uncertainty is likely to be most operationally important (Fig. 1.4A2–D2).

3.2. Population at Risk of *P. vivax* Malaria

Table 1.1 shows our estimates of the population at risk (PAR) of infection and a detailed description of the methodology used to generate these

Figure 1.5, cont'd

estimates is given at the end of this chapter in Section 6. In brief, these estimates were generated by combining maps of the limits of transmission described above with 1 × 1 km resolution gridded population surfaces for 2010 projected from the Global Rural–Urban Mapping Project (GRUMP) year 2000 *beta* version population counts (Balk et al., 2006; CIESIN/ IFPRI/WB/CIAT, 2007). Regional maps of 1 × 1 km gridded population estimates for 2010 are shown in Fig. 1.8. Fine-scale population data were used to ensure the detailed variations in risk level described in our limits maps are appropriately assigned to the underlying population.

3.3. Vectors of the *P. vivax* Parasite

Figure 1.9 shows the distribution of *Anopheles* species considered to be the dominant vector species/species complexes (DVS) of human malaria
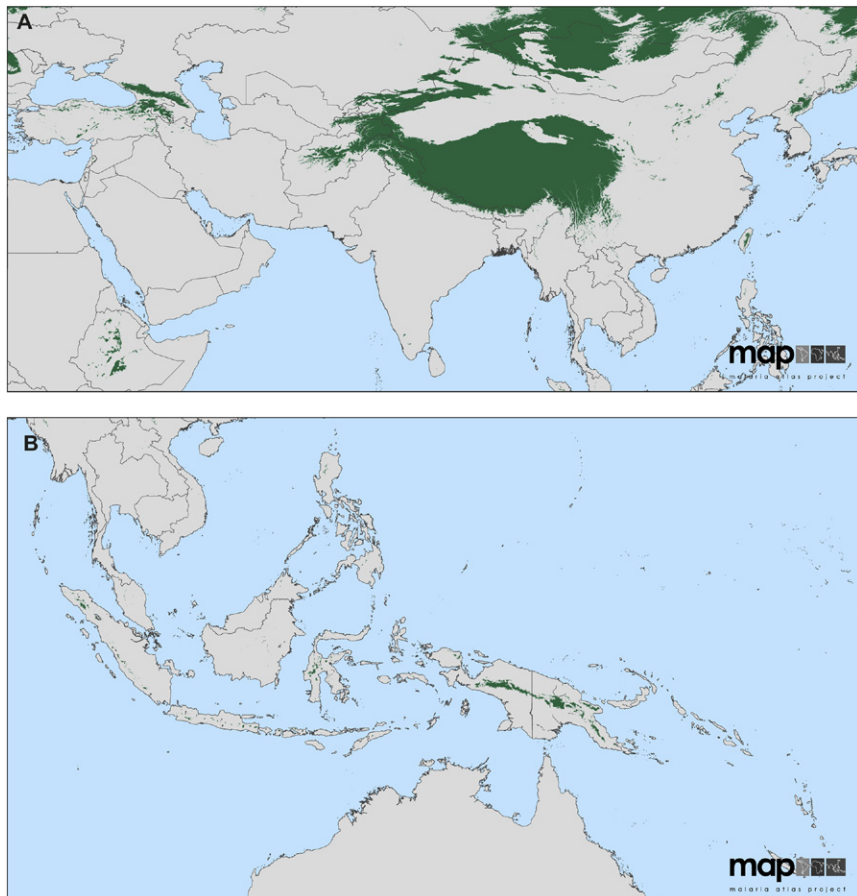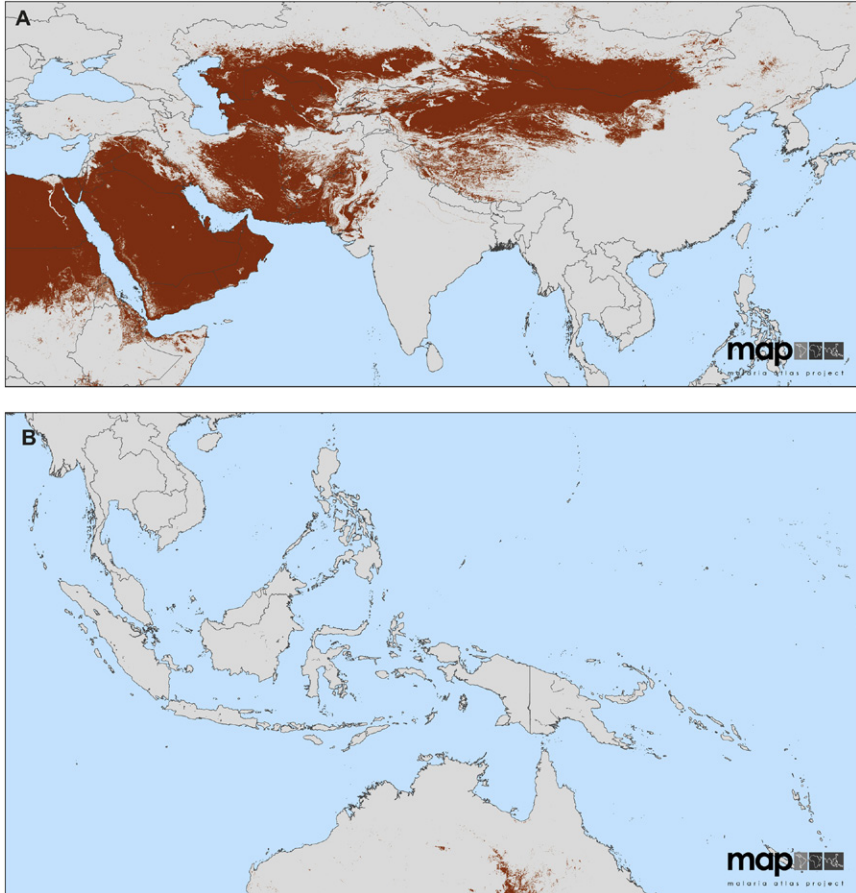
Figure 1.6 Environmental suitability for transmission of *P. vivax* as defined by extreme aridity in Asia, Asia-Pacific, the Americas and Africa+. Areas shaded in brown are those classified as bare areas by the GlobCover land cover product in Asia (A), Asia-Pacific (B), the Americas (C) and Africa+ (D), interpreted as lacking sufficient moisture to support populations of *Anopheles* necessary for transmission. For interpretation of the references to colour in this figure legend, the reader is referred to the online version of this book.

(*P. falciparum* and *P. vivax)* within each region of the world (Sinka et al., 2012), and a detailed description of the methods to generate these maps is given in Section 6.4. In brief, the distribution of each of the dominant species or species complex was individually predicted using occurrence data (mainly abstracted from published surveys), the Boosted Regression Trees (BRT) ecological niche modelling technique (Elith et al., 2008), environmental covariates, and species range expert opinion maps derived from

Figure 1.6, cont'd

consultation with vector experts (Hay et al., 2010c; Sinka et al., 2010a, 2010b, 2011). The resulting maps illustrate the predicted distribution of the DVS using a probability of occurrence metric. While the ecological covariates of the model are based on annualised means of temperature and precipitation, the maps cannot represent the season fluctuations that may occur in the distribution of the DVS, which may be significant in those that extend into temperate climes. Expert opinion was also used to classify the most important species/combinations of species per region (i.e. those with the highest impact) and their individual distributions were overlaid, with the most competent vectors species uppermost, to generate the maps shown. The combined vector map aims to aid vector control planning by showing which species need to be controlled in each area.
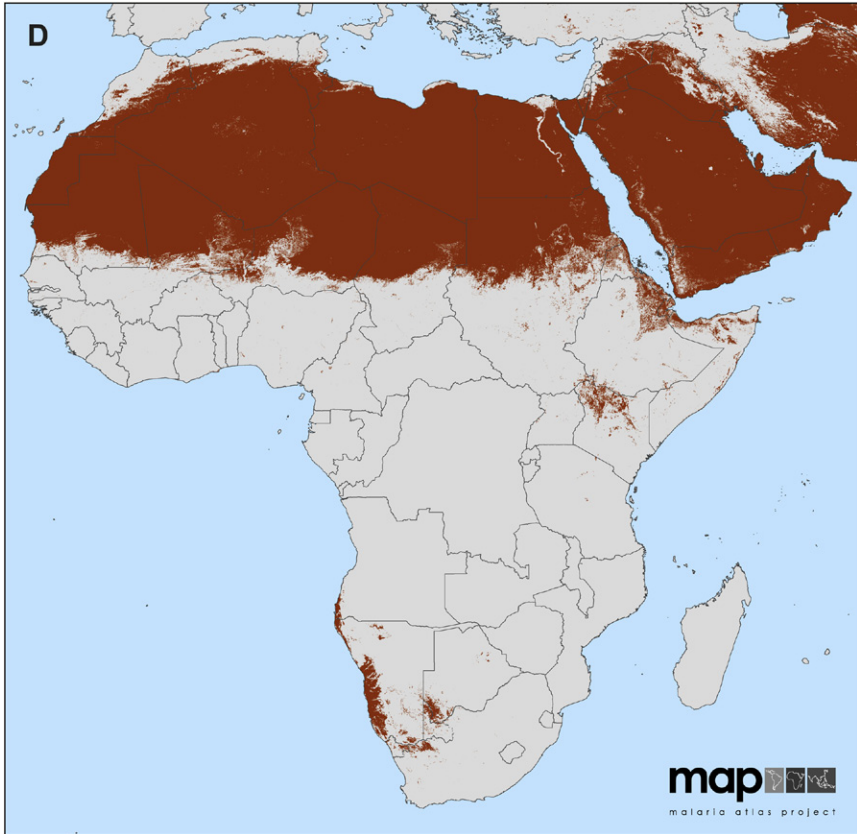
Figure 1.6, cont'd

A species complex is a group of closely related species that are often indistinguishable based on morphology alone. Reference to a complex may be indicated by referring to the species as '*sensu lato*' or '*s.l.*' (e.g. *Anopheles gambiae s.l.*) meaning 'in the broad sense', whereas '*sensu stricto*' or '*s.s.*' ('in the strict sense') indicates the species alone (often a sibling within a species complex has the same name as the complex). The presence of species complexes adds a level of complexity to vector control efforts. Sibling species that are morphologically indistinguishable and often sympatric within an area can have such varied bionomics that one sibling is rendered a dominant vector and the other a non-vector (Meek, 1995; Manguin et al., 2008). The proper identification of species and knowledge of their ranges, often rapidly altered by expanding agriculture and land use changes (Amerasinghe et al., 1991a; Amerasinghe and Indrajith, 1994; Lee, 1998; Singh and Mishra, 2000;
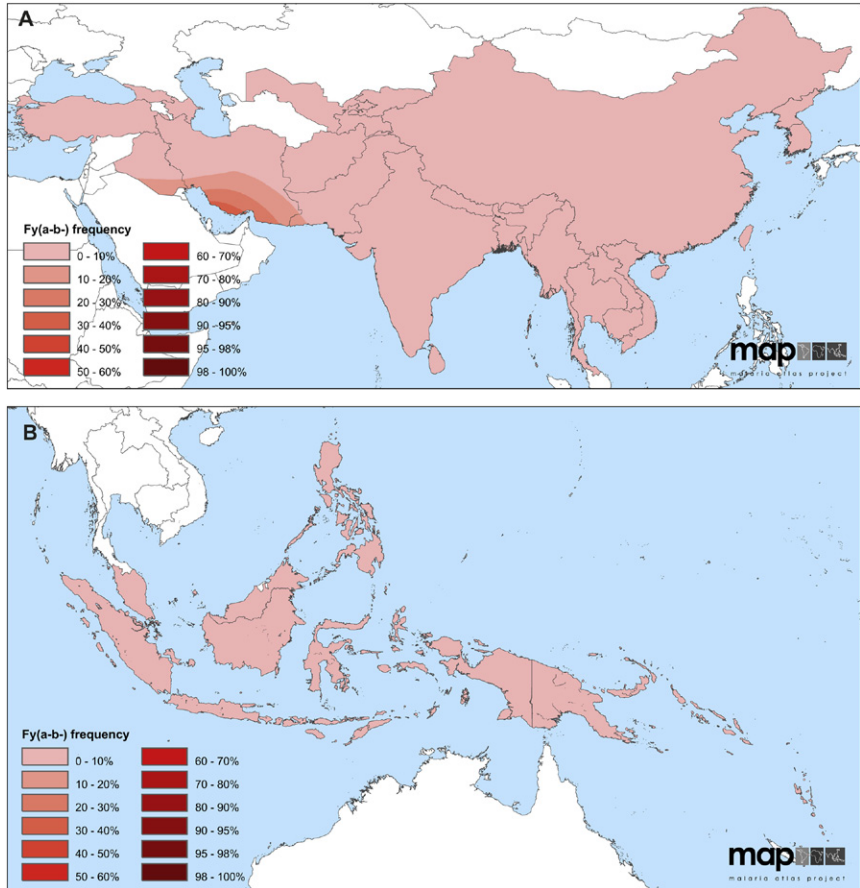
Figure 1.7 Distribution of the Duffy negative phenotype in Asia, Asia-Pacific, the Americas and Africa+. The prevalence of the Duffy-negative phenotype, Fy(a−b−), is shown in Asia (A), Asia-Pacific (B), the Americas (C) and Africa+ (D). The Duffy prevalence model is full described elsewhere (Howes et al., 2011). Only the *Pv*MECs in each region are shown in colour. For a colour version of this figure, the reader is referred to the online version of this book.

Vythilingam et al., 2005), is vital for appropriate allocation of vector control resources.

A search of the current literature has identified 71 species/species complexes with the potential ability to transmit *P. vivax* (Table 1.2), which includes all 41 species classified by Sinka et al. (2010a, 2010b, 2011) as DVS, 34 of which are shown in Fig. 1.9 (a number of species were not included in the global multi-species maps as they were of lesser importance when classified by region and were completely overlaid by higher impacting vectors).
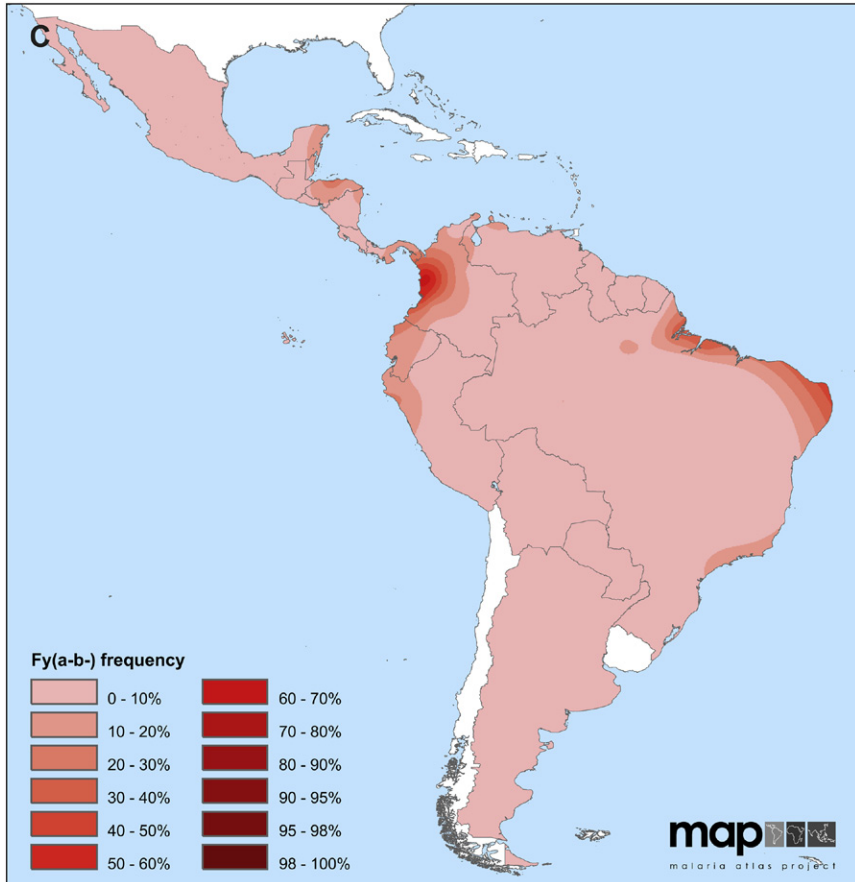
Figure 1.7, cont'd

This suggests, and the literature appears to corroborate, that all vectors capable of transmitting *P. falciparum* are also capable of transmitting *P. vivax*. Interestingly, the reverse (all *P. vivax* vectors being capable of transmitting *P. falciparum*) appears not to hold true.

4. REGIONAL SUMMARIES OF THE PUBLIC HEALTH SIGNIFICANCE OF *P. VIVAX* MALARIA

4.1. Asia

The Asia region (defined for these purposes as mainland Asia but excluding the Malaysian Peninsula; Fig. 1.2) has, amongst the highest endemicity estimates of *P. vivax* malaria globally (Fig. 1.3A2), a diverse range of
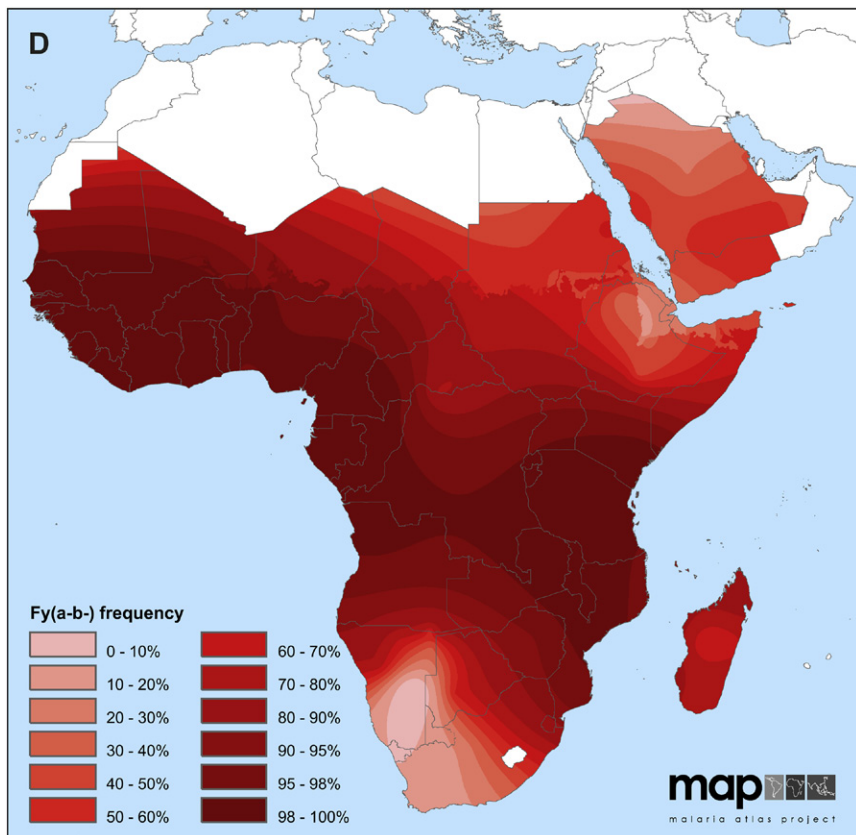
Figure 1.7, cont'd

Table 1.1 Area and Populations at Risk of *Plasmodium vivax* Malaria in 2010

	Area (million km²)			Population (million)		
Region	**Unstable**	**Stable**	**Any risk**	**Unstable**	**Stable**	**Any risk**
America	1.38	8.08	9.46	87.66	49.79	137.45
Africa+	20.60	1.86	22.46	48.72	37.66	86.38
Asia	5.60	3.63	9.24	1236.92	812.55	2049.47
Asia–Pacific	0.96	1.78	2.74	150.17	64.90	215.07
World	28.55	15.34	43.90	1523.47	964.90	2488.37

Risk is stratified into unstable risk (PvAPI < 0.1 per 1000 people p.a.) and stable risk (PvAPI ≥ 0.1 per 1000 people p.a.). America = Central and South America; Africa+ = Africa, Yemen and Saudi Arabia; Asia = mainland Asia excluding the Malaysian Peninsula; Asia–Pacific = southern islands of Asia–Pacific and the Malaysian Peninsula.
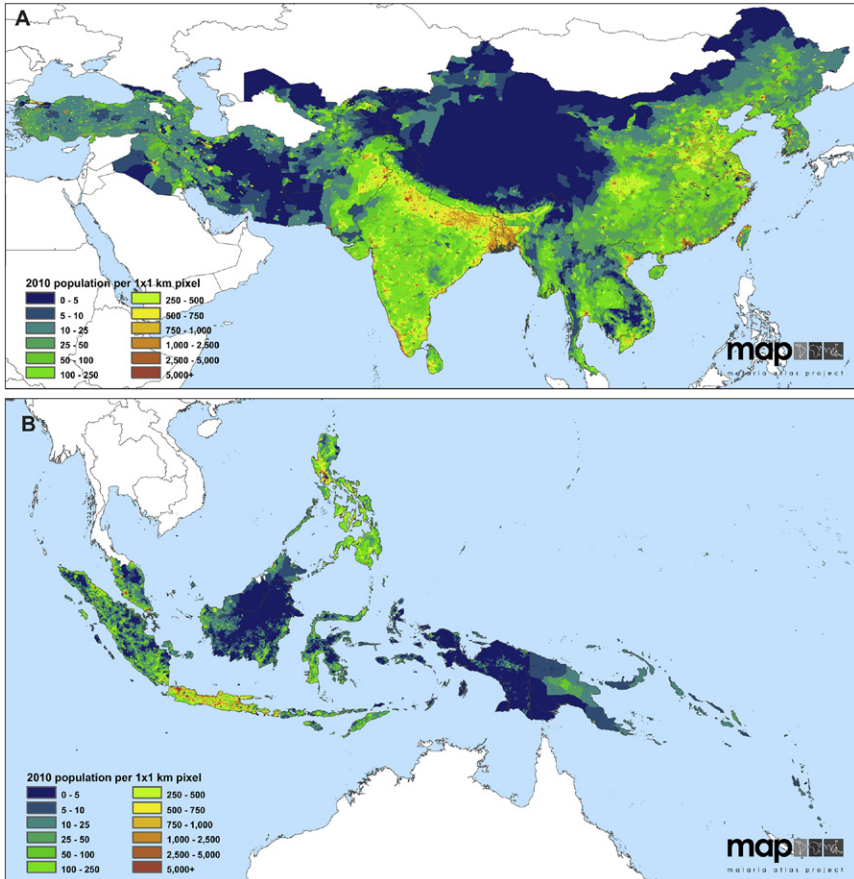
Figure 1.8 Population surfaces for 2010 in Asia, Asia-Pacific, the Americas and Africa+. Population estimates in Asia (A), Asia-Pacific (B), the Americas (C) and Africa+ (D) were estimated from the GRUMP beta 2000 data (Balk et al., 2006; CIESIN/IFPRI/WB/ CIAT, 2007) and are shown here at 0.0083 × 0.0083 decimal degree resolution (0.0083 decimal degrees is approximately equal to 1 km at the equator). Only the *Pv*MECs in each region are shown in colour. For a colour version of this figure, the reader is referred to the online version of this book.

epidemiologically important vectors, and by far the largest populations at risk. A low prevalence of Duffy negativity and high population densities in many of the endemic countries in Asia make it an important global *P. vivax* transmission setting to understand and the vast majority (84%) of the global PAR of stable *P. vivax* transmission live in this region.

    Defining the limits of transmission. API data were available for all coun-tries except Uzbekistan and Democratic People's Republic of Korea (Korea
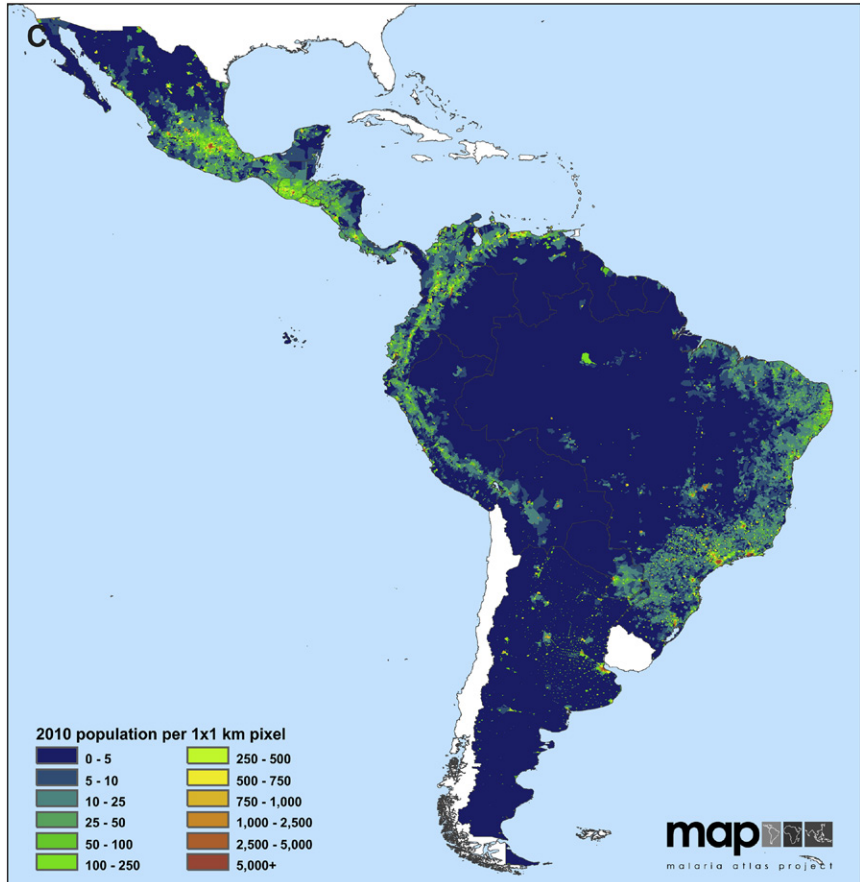
Figure 1.8, cont'd

DPR). Five countries reported data up to the year 2010 (Bhutan, Georgia, Nepal, Sri Lanka and Thailand) with the majority (14/23) providing data up to 2008. India and China's last year of reporting was 2007.

Transmission was estimated to span 9 million square kilometres of land in Asia (around 45% of the total land area in Asia). The majority of this area (61%; 5.60 million km^2) was at unstable risk. The areas at risk in India and China covered 2.97 and 2.82 million km^2 each and, therefore, comprised 63% of the total area at risk in Asia (Panel A1 of Fig. 1.3).

Estimating endemicity. There were 2665 records of prevalence data collected from the region. The three most data-rich countries were Viet Nam ($n = 657$), Afghanistan ($n = 493$) and Bangladesh ($n = 365$), as illustrated in
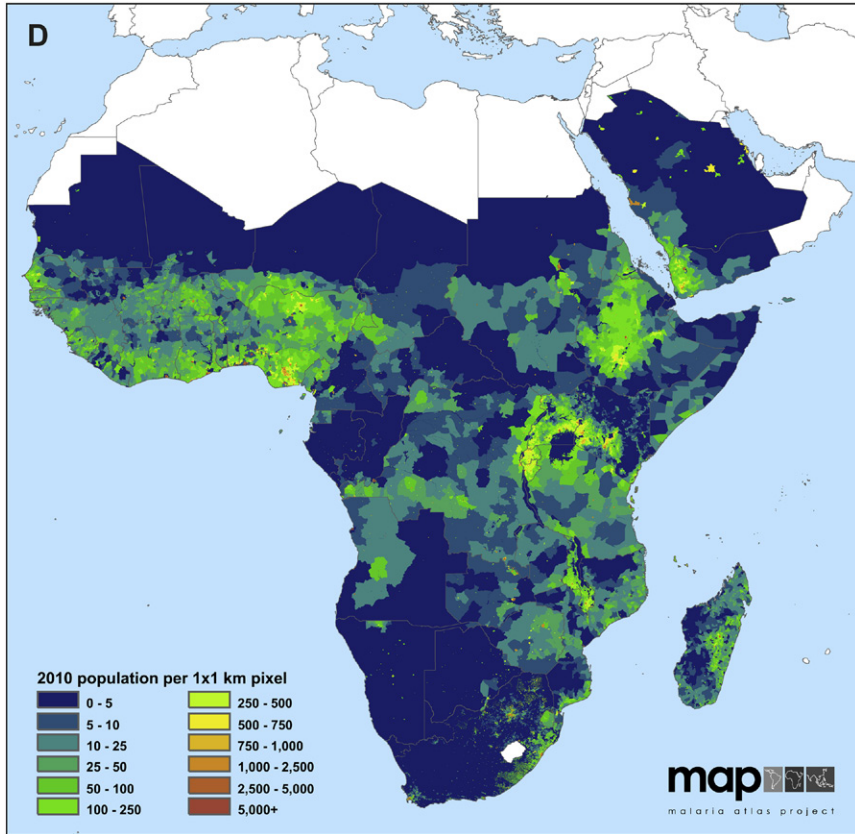
Figure 1.8, cont'd

Panel A1 of Fig. 1.3. The predicted prevalence estimates in stable transmission areas in Asia were highly heterogeneous. Areas with point estimates above 7% were found in small parts of India, Myanmar and Thailand. Regions with $PvPR_{1-99}$ estimates between 3.5 and 7% were found in large areas of India and pockets of China, Myanmar, Thailand, Cambodia and Lao People's Democratic Republic (Lao PDR). Uncertainty maps reveal that areas of high uncertainty correspond with high transmission areas. These areas also had sparse prevalence survey data. Relative to its size, India had very little prevalence data available. Myanmar and Thailand also had large regions with stable transmission but with few surveys to support the prevalence estimates. While predictions on the Korean peninsula were made with relatively high certainty (Fig. 1.4A1), there were no survey data available from Korea DPR. Known prevalence values from this region as well as from India, Myanmar,
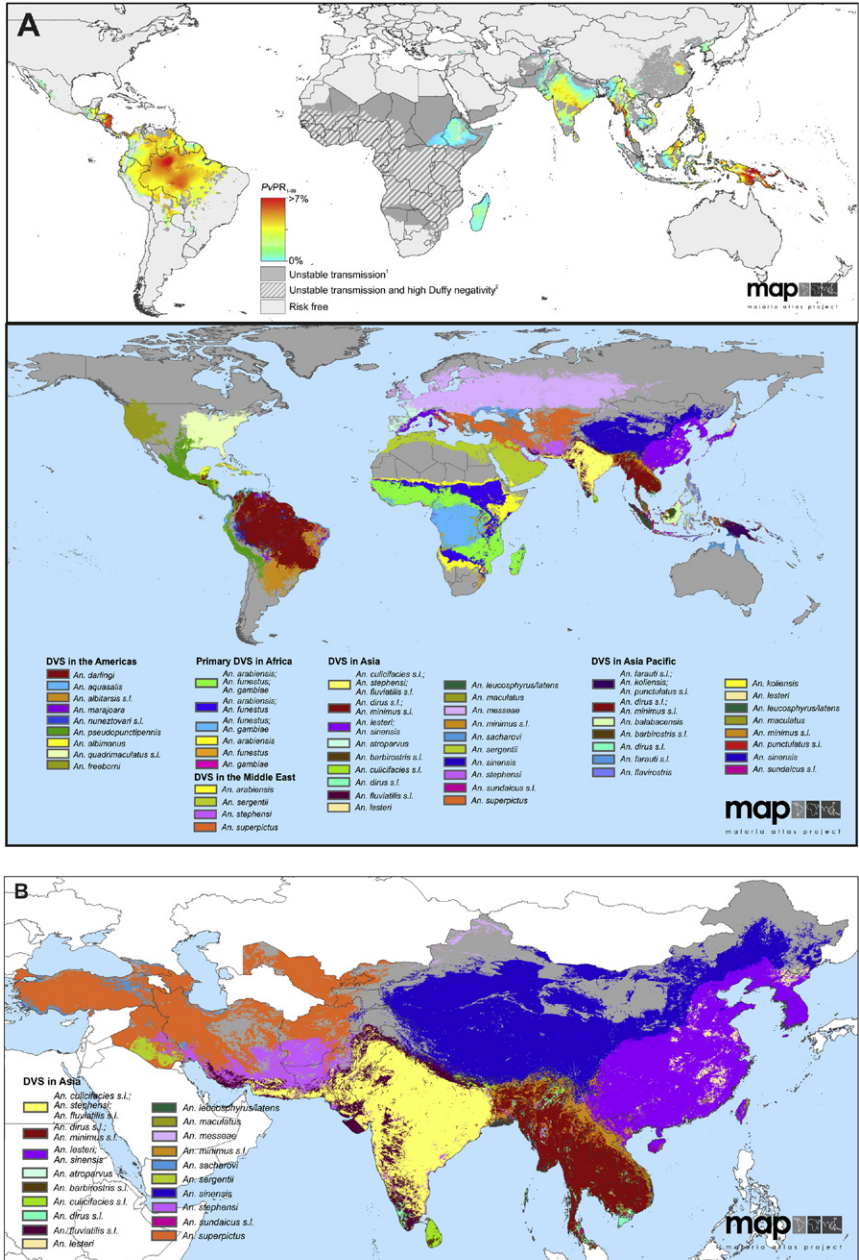
Figure 1.9 Distribution of dominant vector species globally and in Asia, Asia-Pacific, the Americas and Africa+.
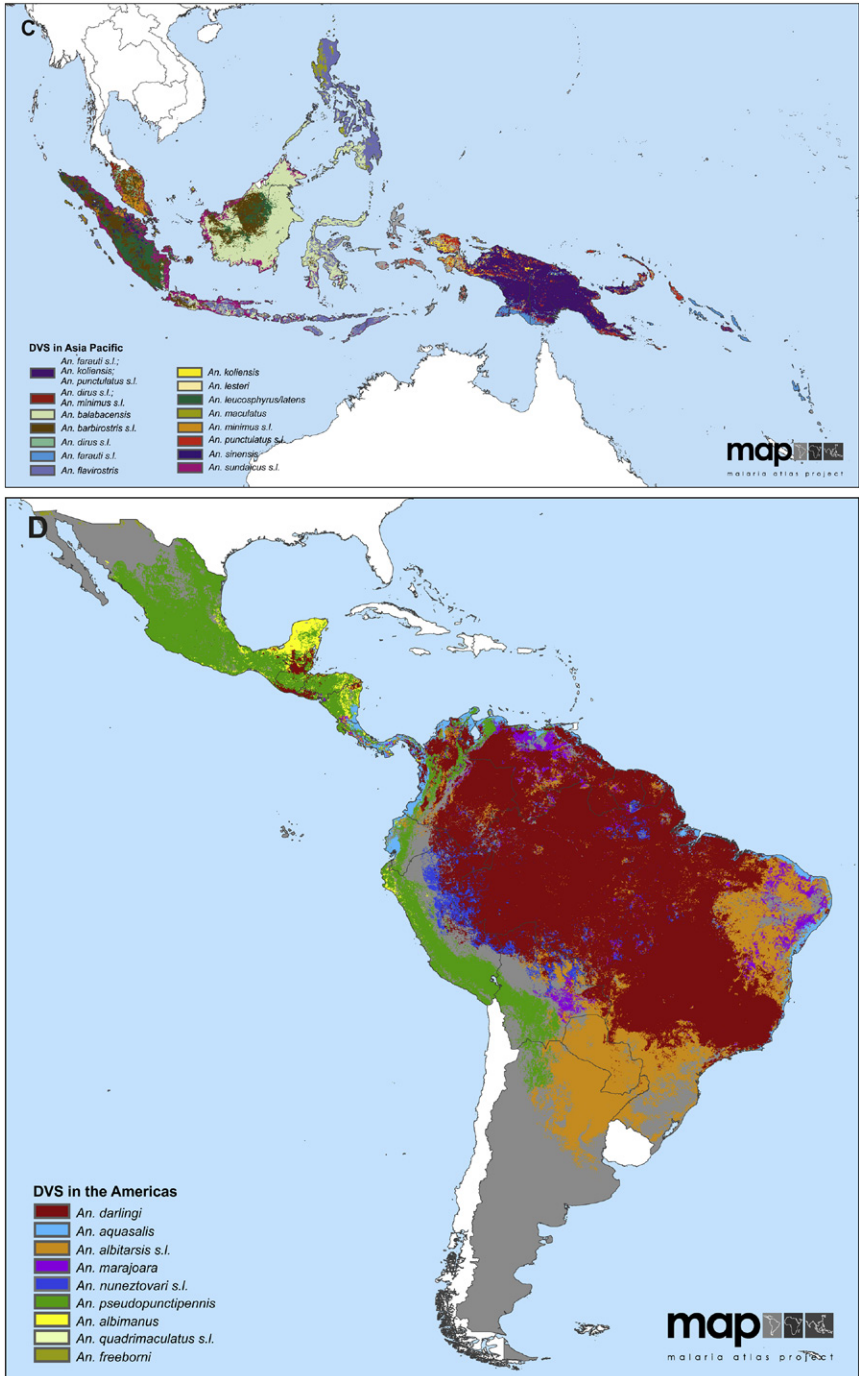
Figure 1.9, cont'd
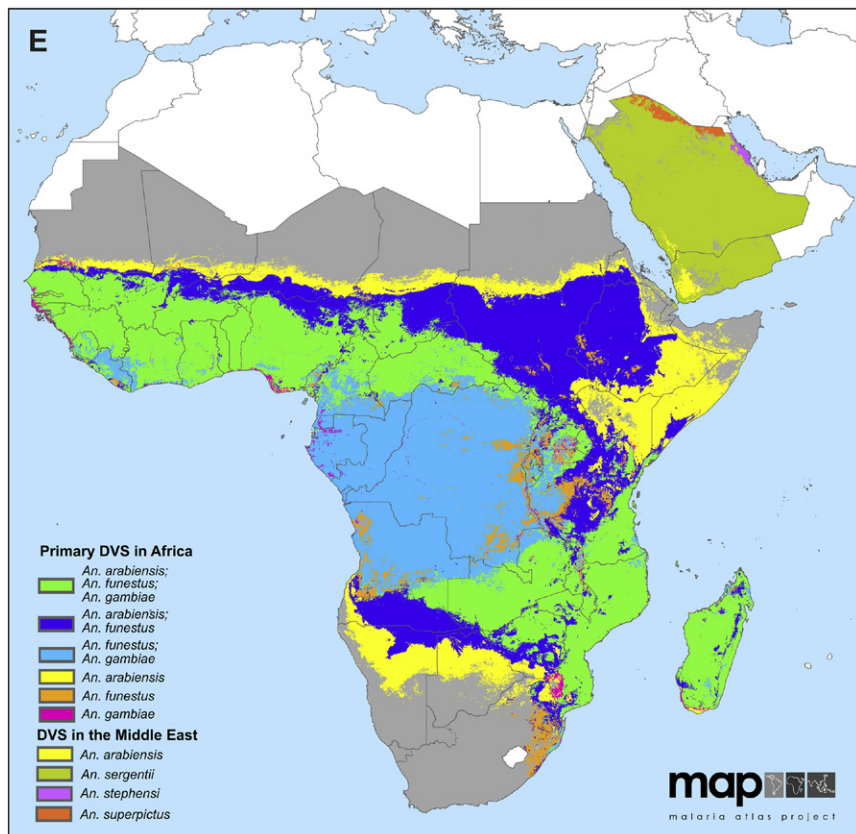
Figure 1.9, cont'd The global distribution of the main dominant vector species is shown in Panel A alongside the predicted endemicity of *P. vivax* in 2010. The distribution of the primary vector species are also shown at the regional level: Asia (B), Asia-Pacific (C), the Americas (D) and Africa+ (non-endemic countries are shaded white). The legend for Africa+ is disaggregated in to Africa and the Middle east because only the primary vector species in Africa are shown in the map. For colour version of this figure, the reader is referred to the online version of this book.

Thailand and parts of China with stable vivax transmission would improve the certainty of PvPR$_{1-99}$ predictions for the area as a whole. Regions with low endemicity and high density of surveys, such as Afghanistan, Cambodia and the small region with stable transmission in Turkey, were predicted with high certainty. The population–weighted uncertainty map differs substan–tially for parts of this region (Fig. 1.4A2). Incorporating population esti–mates allows weighting to highlight areas where high uncertainty and large populations coincide. Thus, sparsely populated areas of Myanmar, Thailand,

Cambodia, Lao PDR, Viet Nam and Korea DPR displayed small values of this index despite uncertain predictions of prevalence. Conversely, values for highly populated areas across India, parts of Pakistan and the stable transmission region in China, were inflated substantially. Predictions in this region would be best improved, therefore, with more detailed prevalence data from these population centres.

Population at risk. The PAR in Asia was, by far, the largest of all of the regions due to large areas of risk and high population densities. There were over two billion people living at risk in this region in 2010, which constituted 82% of the total global PAR. The greatest PAR was found in India, China and Pakistan with 1.13 billion, 462 and 169 million at risk, respectively. India's PAR comprised more than half (55%) of the Asia-region PAR. Together, China and Pakistan made up another 30% (23 and 8%, respectively), indicating that 85% of the region's PAR was attributable to three nations. These nations also had the largest populations in this region. Compared to India and Pakistan, a smaller proportion of China's overall population was living at risk of *P. vivax*. Of China's estimated 1.4 billion people, 33% were at risk of *P. vivax*, whereas 95% of India's 1.2 billion and 90% of Pakistan's 188 million people were living at some level of risk. When we consider both levels of risk (unstable and stable transmission), we find that 60%, or 1.2 billion, of the PAR in Asia experienced unstable risk, indicating that over 800 million individuals in this region lived in stable transmission areas. Countries devoid of stable transmission areas were Iraq, Kyrgyzstan and Uzbekistan. Countries with the greatest population at stable risk in this region were again India (642.07 million), Pakistan (43.82 million) and China (31.92 million). Other countries that had large (>10 million) PAR living in stable transmission areas were Korea DPR (21.07 million), Myanmar (20.48 million), Thailand (17.11 million) and Bangladesh (16.04 million). Ninety eight percent of the population living in stable transmission areas was, therefore, found in 30% (7 out of 24) of the countries in Asia.

Vectors. Of the 35 potential *P. vivax* vector species found within Asia as a whole (Table 1.2), there are 19 DVS (Sinka et al., 2011) of which, at least seven are considered to be species complexes (Harbach, 2004). Nine DVS are found solely in the Asia region, whilst the remaining 10 have distributions extending into the Asia–Pacific region.

A total of 10,667 unique occurrence points were georeferenced for the 19 DVS across Asia. Records of species occurrence obtained from observations recorded to point (≤10 km^2) and wide area (10–25 km^2) locations

(sites) were used for analyses. In some cases, more than one occurrence point was obtained for a single site. The greatest number of points were found for the *Anopheles culicifacies* complex (*n* = 1568) followed by the *Anopheles subpictus* (*n* = 1143) and *Anopheles barbirostris* (*n* = 1064) complexes. From the 15 Asian *P. vivax* malaria endemic countries (*Pv*MECs), where anopheline occurrence data were found, data were obtained from 5388 sites. The greatest number of sites were in Myanmar (*n* = 1830), India (*n* = 1529) and China (*n* = 355). There was only one reported occurrence located in Turkey.

The predicted distributions of the DVS in Asia resulted in a complex multi-species map, where the main vector species overlap over large areas of land and exist independently in small areas (Fig. 1.9B). It is beyond the scope of this review to describe the individual distributions and bionomics of the 19 potential DVS in this region, however, a complete discussion of the ranges and bionomics of the global DVS may be found elsewhere (Sinka et al., 2010a, 2010b, 2011, 2012). The DVS described in the following paragraphs are those that were deemed to be primary malaria vectors by the project's technical advisory group (TAG), which are therefore shown prominently in Fig. 1.9A, and showed conclusive evidence for the ability to transmit *P. vivax* (Table 1.2). The potential primary DVS that met these criteria were the *An. culicifacies* complex (Culicifacies Complex; *An. culicifacies s.l.*), the *Anopheles dirus* complex (Dirus Complex; *An. dirus s.l.*), the *Anopheles minimus* complex (Minimus Complex; *An. minimus s.l.*), *Anopheles sinensis*, *Anopheles stephensi* and *Anopheles superpictus*.

Anopheles culicifacies s.l. is a prominent vector across the Indian subcontinent, found in sympatry with *An. stephensi* and *Anopheles fluviatilis s.l.* Species B of the Culicifacies Complex is considered a non-vector of *P. falciparum*, currently attributed to highly zoophilic behaviour. However, there is evidence shown in Table 1.2 that the species is also partially refractory to *P. vivax* and, hence, perhaps to malaria parasites overall (Adak et al., 2005; Vijay et al., 2011). Evidence of wild-infected populations and experimental infections suggest that at least species A and C of the complex are primary vectors of malaria on the Indian subcontinent. Bangladesh, Myanmar, Thailand, Cambodia, Lao PDR and Viet Nam are dominated by the Dirus and Minimus Complexes (Fig. 1.9B). The range of the *An. sinensis* complex covers the majority of China, where it is shown to co-exist with *Anopheles lesteri* along the eastern areas of the country and the Korean peninsula. However, the overlapping distributions of these two vector species may be an artefact of mis-identification in some areas rather than true sympatry

Table 1.2 Known and potential vector species of *Plasmodium vivax*

Species, species complex* or group	Distribution and bionomics reviewed by MAP†	*P. vivax* vector (Yes/No)‡	Notes and reference(s)
Asia			
An. atroparvus van Thiel	Yes	Yes(?)	*An. atroparvus* has been shown to be experimentally infected with *P. vivax* by humans (Daskova and Rasnicyn, 1982) and (Collins et al., 1980; Collins et al., 2009). This species has been shown to be refractory to *P. falciparum* infection (de Zulueta et al., 1975; Daskova and Rasnicyn, 1982; Romi et al., 2001).
An. baimaii Sallum & Peyton	Yes (part of the *An. dirus* complex)	Yes(?)	*P. vivax* and *P. falciparum* are commonly found in *An. baimaii* (Sallum et al., 2005; Obsomer et al., 2007), but original sources do not differentiate the members of the Dirus Complex (Prakash et al., 2001).
An. culicifacies complex	Yes	Yes	Naturally *P. vivax*-infected *An. culicifacies* were found in Madhya Pradesh (Species C and D) (Subbarao et al., 1992) and Uttar Pradesh (Species A) (Subbarao et al., 1988) in India, and in Sri Lanka (Amerasinghe et al., 1991b). *An. culicifacies* have been experimentally infected with *P. vivax* in from infected monkeys (Collins et al., 2009) and laboratory colonies established from wild caught *An. culicifacies* (Species A, B and C) were infected with vivax from blood drawn from infected humans (Adak et al., 1999). Species A and C showed relatively high oocyst infections but Species B did not. Sporozoite infections were relatively high in Species A compared to Species C and negligible in Species B. There is evidence that Species B may be refractory to *P. vivax* infection (Adak et al., 2006; Vijay et al., 2011).
An. fluviatilis complex	Yes	Yes(?)	Sporozoites were detected in specimens collected in Iran and the species is said to transmit both *P. vivax* and *P. falciparum* (Eshghi et al., 1976). Both oocytes and sporozoites were found in an *An. fluviatilis* (Species T) laboratory colony infected by human volunteers under controlled conditions (Adak et al., 2005).

Hyracanus Group	No	Yes	Wild *P. vivax*-infected Hyracanus Group mosquitoes were found in Assam, India (Rattanarithikul et al., 1996; Prakash et al., 2004).
An. messeae Falleroni	Yes	Yes(?)	*An. messeae* was implicated as a vector of *P. vivax* in eighteenth and nineteenth century Finland (Hulden et al., 2008; Hulden, 2009) and the authors refer to evidence of *An. messeae* as a vector in Russia (Sokolova and Snow, 2002), but only indirect evidence linking malaria incidence with vector density was provided.
An. nimpe Nguyen, Tran & Harbach	No (part of the Hyracanus Group)	Yes(?)	*An. nimpe* was implicated as a vector (Nguyen et al., 2000) of *P. vivax* and *P. falciparum* after being sampled in coastal Viet Nam, but direct evidence of infection was not available.
An. philippinensis-nivipes complex	No	Yes	Wild-infected *An. philippinensis-nivipes s.l.* specimens were found to be positive for *P. vivax* in Assam, India (Prakash et al., 2004).
An. pulcherrimus Theobald	No	Yes	*An. pulcherrimus* is thought to be the main vector in Afghanistan (Brooker et al., 2006). *Plasmodium vivax* (VK210 and VK247 subtypes) was detected in specimens collected in Afghanistan (Rowland et al., 2002) and *P. vivax* circumsporozoite proteins were detected though enzyme-linked immuno-sorbent assay (ELISA) in wild-infected wild-infected mosquitoes (the vast majority of which were *An. pulcherrimus*), but the authors do not explicitly state that *P. vivax* was found in *An. pulcherrimus* (Faulde et al., 2007).
An. sacharovi Favre	Yes (part of the Maculipennis Subgroup)	Yes	*P. vivax* circumsporozoite antigens were detected in wild populations sampled in Turkey (Simsek et al., 2010). *P. vivax* oocysts and sporozoites were detected in the salivary glands of a laboratory colony of *An. sacharovi* fed on vivax infected humans (Kasap, 1990).
An. sawadwongporni Rattanarithikul & Green	No (part of the Maculatus Group)	Yes	*P. vivax* (VK247) was detected in specimens collected in Thailand (Coleman et al., 2002).
An. sergentii (Theobald)	Yes	Yes	*P. vivax* circumsporozoite proteins were detected in *An. sergentii* specimens sampled from desert oases in Egypt (Kenawy et al., 1990).

Continued

Table 1.2 Known and potential vector species of *Plasmodium vivax*—*cont'd*

Species, species complex* or group	Distribution and bionomics reviewed by MAP[†]	*P. vivax* vector (Yes/No)[‡]	Notes and reference(s)
An. stephensi Liston	Yes	Yes	*P. vivax* (VK210 and VK247) was detected in specimens collected in Afghanistan (Rowland et al., 2002). *An. stephensi* has been experimentally infected with *P. vivax* from infected monkeys (Basseri et al., 2008; Collins et al., 2009) and humans (Adak et al., 2005); both oocysts and sporozoites found were found in the mosquitoes.
An. superpictus Grassi	Yes	Yes	*P. vivax* (VK247) was detected in specimens collected in Afghanistan (Rowland et al., 2002). Laboratory colonies *An. superpictus* have been infected with *P. vivax*-infected humans; oocysts and sporozoites were in salivary glands (Kasap, 1990). This species seems to be generally implicated as a vivax vector in other articles.
An. varuna Iyengar	No (part of the Aconitus Subgroup)	Yes	Wild-infected mosquitoes were found to be positive for *P. vivax* in Assam, India (Prakash et al., 2004).

Asia and Asia-Pacific

An. aconitus Dönitz	Yes	Yes	*P. vivax* sporozoites have been detected (by ELISA) in wild captured *An. aconitus* in Sri Lanka (Amerasinghe et al., 1991b). Laboratory studies revealed that *An. aconitus* forms B and C were susceptible to *P. vivax* and *P. falciparum*, and that *An. aconitus* form C was susceptible only to *P. vivax* (Junkum et al., 2005).
An. annularis van der Wulp	Yes	Yes	*P. vivax* sporozoites have been detected (by ELISA) in wild captured *An. annularis* in Sri Lanka (Amerasinghe et al., 1991b) and India (Prakash et al., 2004).
An. barbirostris complex	Yes	Yes	*P. vivax* circumsporozoite proteins were found in specimens collected in Thailand with infectivity rates of 0.24% (Rattanarithikul et al., 1996) and 4.8% (Frances et al., 1996).

An. campestris Reid	No	Yes	*P. vivax* (VK210) was detected in specimens collected in Thailand (Coleman et al., 2002).
An. dirus complex	Yes	Yes	*P. vivax* circumsporozoite proteins have been detected in an *An. dirus* specimen collected in Thailand (Baker et al., 1987). The vectorial capacity of *An. dirus* for *P. vivax* has been estimated (Prakash et al., 2001). Experimental infection from humans (Wirtz et al., 1985), monkeys (Collins et al., 2009) and membrane feeding has been shown (Coleman et al., 2004; Junkum et al., 2005).
An. donaldi Reid	No	Yes	*P. vivax* circumsporozoite proteins have been detected in *An. donaldi* specimens sampled in Malaysia (Seng et al., 1999). *An. donaldi* was successfully infected with *P. vivax* and *P. falciparum* sporozoites in the lab and was capable of transmitting both species to man (Hardin et al., 1973; Harrison and Scanlon, 1975).
An. hodgkini Reid	No	Yes	*P. vivax* was detected in specimens collected in Thailand (VK247) (Coleman et al., 2002).
An. karwari (James)	No	Yes	*P. vivax* circumsporozoite proteins in *An. karwari* specimens collected in Thailand (Frances et al., 1996).
An. kochi Dönitz	No	Yes	Wild *P. vivax*-infected *An. kochi* mosquitoes were found in Assam, India (Prakash et al., 2004).
An. lesteri Baisas & Hu (synonymous with *An. anthropophagus* Xu & Feng)	Yes	Yes(?)	*An. lesteri* (*An. anthropophagus*) were experimentally infected with *P. vivax* from humans in Republic of Korea (Shin et al., 2002). Human laboratory feedings showed *An. lesteri* to be a highly competent vector (Joshi et al., 2009).
An. letifer Sandosham	No	Yes(?)	Specimens collected in Sarawak, Malaysia were found to be sporozoite positive and although the species of the parasite was not identified, >90% of the malaria infections in the region at the time were due to *P. vivax* (Chang et al., 1997). Implied transmission, but with no direct evidence, is described in other references (Rahman et al., 1997; Fryauff et al., 1998).

Continued

Table 1.2 Known and potential vector species of *Plasmodium vivax—cont'd*

Species, species complex* or group	Distribution and bionomics reviewed by MAP†	*P. vivax* vector (Yes/No)‡	Notes and reference(s)
An. leucosphyrus Dönitz & *An. latens* Sallum & Peyton	Yes (sister species in the Leuco-sphyrus Com-plex)	Yes	*P. vivax* circumsporozoite proteins have been detected in *An. leucosphyrus* specimens sampled in Malaysia (Seng et al., 1999). However, the species sampled was most likely *An. latens*, which was commonly misidentified as its sister species *An. leucosphyrus* (Sallum et al., 2005).
An. ludlowae (Theobald)	No	?	No references were found to confirm that *An. ludlowae* transmits *P. vivax*, but it is a potential vector in areas where vivax malaria is found (e.g. the Philippines and Indonesia) (Lien et al., 1977; Wooster and Rivera, 1985).
An. minimus complex	Yes	Yes	*P. vivax* was detected in specimens collected in Thailand (VK210 and VK247) (Coleman et al., 2002) and India (VK247) (Prakash et al., 2004). *An. minimus* has also been experimentally infected with *P. vivax* from monkeys (Rattanarithikul et al., 1996; Collins et al., 2009).
An. nigerrimus Giles	No	Yes	*P. vivax* (VK210) circumsporozoite proteins have been detected in *An. nigerrimus* sampled in China (Alam et al., 2010) and *An. nigerrimus* has been incriminated as a vector there (WHO, 1986).
An. sinensis Wiedemann	Yes (part of the Hyracanus Group)	Yes	*P. vivax* (VK210 and VK247) was detected in specimens collected in the Republic of Korea (Lee et al., 2002). Deliberate infection was also observed in laboratory conditions (Shin et al., 2002).
An. subpictus complex	Yes	Yes	*P. vivax* circumsporozoite proteins have been detected in *An. subpictus* sampled in Sri Lanka (Amerasinghe et al., 1991a).
An. sundaicus complex	Yes	Yes(?)	*An. sundaicus* is described as a vector of primarily *P. falciparum* malaria, implying that it will also transmit *P. vivax* (Am et al., 1993) and *P. vivax* oocysts and sporozoites have been found in infected laboratory colonies (Adak et al., 2005).

An. tessellatus Theobald	No	Yes	*P. vivax* circumsporozoite proteins were detected in *An. tessellatus* species sampled in Sri Lanka (Amerasinghe et al., 1991a).
An. vagus Dönitz	No	Yes	*P. vivax* sporozoites have been detected (by ELISA) in wild captured *An. aconitus* in Sri Lanka (Amerasinghe et al., 1991a) and India (Prakash et al., 2004).

Asia-Pacific

An. balabacensis Baisas	Yes (part of the *An. leucosphyrus* complex)	Yes(?)	Sporozoites were found in specimens collected in Central Java, Indonesia (Barcus et al., 2002) and Palawan, Philippines (Schultz, 1992). Laboratory reports indicate transmission of *P. vivax* to non-human primates (Collins et al., 1980).
An. farauti complex	Yes	Yes	*P. vivax* circumsporozoite proteins were found in specimens collected in Papua New Guinea (Burkot et al., 1988).
An. flavirostris (Ludlow)	Yes	?	*An. flavirostris* has been described as the 'principal vector' in the Philippines, where *P. vivax* and *P. falciparum* malaria occur (Foley et al., 2003) and has been found with sporozoites in Malaysia (Hii et al., 1985) and the Philippines (Oberst et al., 1988), but the parasite species was not given.
An. koliensis Owen	Yes (part of the Punctulatus Group)	Yes	*P. vivax* circumsporozoite positivity of 0.76% was reported for wild-infected *An. koliensis* in Papua New Guinea (Attenborough et al., 1997).
An. maculatus Theobald/Maculatus Group	Yes	Yes	*P. vivax* (VK210 and VK247) was detected in *An. maculatus* specimens collected in Thailand (Coleman et al., 2002). *An. maculatus* has been experimentally infected with *P. vivax* from monkeys (Wirtz et al., 1985; Collins et al., 2009) with a reported infectivity of 4.8% (Collins et al., 1980).
An. punctulatus complex	Yes	Yes	*P. vivax* circumsporozoite antigens were detected in wild populations of the *An. punctulatus* complex sampled in Papua New Guinea (Burkot et al., 1988).

Continued

Table 1.2 Known and potential vector species of *Plasmodium vivax—cont'd*

Species, species complex* or group	Distribution and bionomics reviewed by MAP[†]	*P. vivax* vector (Yes/No)[‡]	Notes and reference(s)
The Americas			
An. albimanus Wiedemann	Yes	Yes	*P. vivax* sporozoites have been detected (by ELISA) in wild captured *An. albimanus* in Mexico (Ramsey et al., 1994) and in specimens experimentally infected from humans (Wirtz et al., 1985). Experimental feeding on monkeys revealed that *An. albimanus* was much more susceptible to 'New World' *P. vivax* (*P. vivax* specimens from Central and South America; 21.2% infection rate), than 'Old World' *P. vivax* (0.4% infection rate) (Li et al., 2001). Other laboratory studies using monkeys showed infectivity rates of only 0.6–0.7% (Collins et al., 1980).
An. albitarsis complex	Yes	Yes	*P. vivax* infection was detected (by dissection to find presence and ELISA to determine *Plasmodium* species) in wild captured *An. albitarsis* in Northern Brazil (de Arruda et al., 1986). Mosquito oocyst infection was observed in laboratory conditions after feeding on infected human volunteers; sporozoites were found in the salivary glands approximately two weeks after feeding (Klein et al., 1991). *P. vivax* infection was also seen in mosquitoes experimentally fed on infected monkeys (Collins et al., 1985).
An. aquasalis Curry	Yes	Yes	*P. vivax* sporozoites have been detected by ELISA in wild captured *An. aquasalis* in Brazil (Povoa et al., 2003). *An. aquasalis* has been experimentally infected with *P. vivax* from infected humans (da Silva et al., 2006).
An. argyritarsis Robineau–Desvoidy	No	Yes(?)	*An. argyritarsis* naturally infected with *P. vivax* have been found in Argentina and the species is identified as a principal vector in parts of Brazil. However, there is some debate whether the species sampled were *An. argyritarsis* or misidentified *An. darlingi* specimens (Linthicum, 1988).

An. bellator Dyar & Knab	No	Yes(?)	*An. bellator* has been found with *P. vivax* oocysts or both oocysts and sporozoites in Brazil (Deane, 1986) and have been experimentally infected from an infected human (Rozeboom and Laird, 1942).
An. benarrochi Gabaldón	No	Yes(?)	Naturally *P. vivax* infected *An. benarrochi* were observed in Peru (Flores-Mendoza et al., 2004), however when mosquito oocyst infection was observed in laboratory conditions after feeding on infected human volunteers, no sporozoites were found in the salivary glands approximately two weeks after feeding (Klein et al., 1991).
An. braziliensis (Chagas)	No	Yes(?)	Naturally *P. vivax* infected *An. braziliensis* were observed in Brazil (da Silva-Vasconcelos et al., 2002), however when mosquito oocyst infection was observed in laboratory conditions after feeding on infected human volunteers; no sporozoites were found in the salivary glands approximately two weeks after feeding (Klein et al., 1991).
An. cruzii Dyar & Knab	No	Yes	*P. vivax* (VK247) infectivity rates of 0.086–0.179% in wild-infected mosquitoes were reported in Brazil (Branquinho et al., 1997).
An. darlingi Root	Yes	Yes	*An. darlingi* specimens were found to be naturally infected with *P. vivax* in Amapa (Conn et al., 2002) and Para States (by dissection to find presence and ELISA to determine *Plasmodium* species) (de Arruda et al., 1986) in Brazil and in French Guiana (Girod et al., 2008). Mosquito oocyst infection was observed in laboratory conditions after feeding on infected human volunteers; sporozoites were found in the salivary glands approximately two weeks after feeding (Klein et al., 1991).
An. deaneorum Rosa-Freitas	No (part of *An. albitaris* complex)	Yes	*An. deaneorum* is a sibling of *An. albitaris* complex and may be an important vector in Amazonian Brazil (Conn et al., 2002). This species can be experimentally infected by both *P. vivax* and *P. falciparum* (Klein et al., 1991; Senise et al., 2006).
An. freeborni Aitken	Yes	Yes(?)	*An. freeborni* has been experimentally infected with *P. vivax* from humans (Burgess and Young, 1950) and monkeys (Collins *et al.*, 2009).

Continued

Table 1.2 Known and potential vector species of *Plasmodium vivax*—cont'd

Species, species complex* or group	Distribution and bionomics reviewed by MAP[†]	*P. vivax* vector (Yes/No)[‡]	Notes and reference(s)
An. hermsi Barr & Guptavanj	No	Yes(?)	*An. hermsi* has been implicated in outbreaks of *P. vivax* in California (Maldonado et al., 1990; Ginsberg, 1991) and *An. hermsi* has been experimentally infected with vivax from monkeys (Collins et al., 2009).
An. marajoara Galvão & Damasceno	Yes (part of the *An. albitarsis* complex)	Yes	Specimens of *An. marajoara* (a sibling of *An. albitarsis s.l.*) collected in Amapa State, Brazil were found to be naturally infected with vivax and may be a superior vector for this parasite over *An. darlingi* in this location (Conn et al., 2002).
An. mediopunctatus Lutz	No	Yes(?)	Mosquito oocyst infection was observed in laboratory conditions after feeding on infected human volunteers and *P. vivax* sporozoites were found in the salivary glands approximately two weeks after feeding (Klein et al., 1991), however other literature states that this species was present in low numbers (de Arruda et al., 1986) or was a non-vector (Vittor et al., 2006).
An. nuneztovari complex	Yes	Yes	*P. vivax* infection was detected in wild captured *An. nuneztovari* by dissection and ELISA was used to determine *Plasmodium* species in Para State, Northern Brazil (de Arruda et al., 1986).
An. oswaldoi Peryassú	No	Yes	*An. oswaldoi* was incriminated as a vector of *P. vivax* in Southern Colombia (Quinones et al., 2006) and Northern Brazil (de Arruda et al., 1986). Mosquito oocyst infection was observed in laboratory conditions after feeding on infected human volunteers and *P. vivax* sporozoites were found in the salivary glands approximately two weeks after feeding (Klein et al., 1991).

An. pseudopuncti-pennis complex	Yes	Yes(?)	*An. pseudopunctipennis* is implied as the vector of *P. vivax* in Bolivia (Lardeux et al., 2007) and has been experimentally infected with *P. vivax* with variable infectivity rates from different vivax strains (Rodriguez et al., 2000). While natural infections with *P. vivax* have been reported from Argentina and Mexico (Warren et al., 1980), there is also evidence of *Plasmodium* sporozoites being absent from *An. pseudopunctipennis* populations in Belize (Achee et al., 2000) and El Salvador (Warren et al., 1980) and experiments have shown *An. pseudopunctipennis* to be refractory to *P. vivax* (VK210) (Gonzalez-Ceron et al., 2007).
An. punctimacula Dyar & Knab	No	Yes	Experimental man–to-mosquito transmission has been confirmed, and naturally infected *An. punctimacula* have been found in Panama (Simmons, 1937; Quinones et al., 2006; Ulloa et al., 2006; Loaiza et al., 2008).
An. quadrimaculatus complex	Yes	Yes(?)	Species of the *An. quadrimaculatus* are implied to be vectors of *P. vivax* malaria (Jensen et al., 1996) and has been infected in the laboratory from *P. vivax*-infected monkeys (Collins et al., 2009).
An. triannulatus Neiva & Pinto	No	Yes	*P. vivax* was detected in wild captured *An. triannulatus* in Para State, Northern Brazil (de Arruda et al., 1986). Mosquito oocyst infection was observed in laboratory conditions after feeding on infected human volunteers and *P. vivax* sporozoites were found in the salivary glands approximately two weeks after feeding (Klein et al., 1991).

Africa+

An. arabiensis Patton	Yes (part of the *An. gambiae* complex)	Yes	*P. vivax* sporozoites have been detected (by ELISA) in wild captured *An. arabiensis* in Southern Ethiopia (Taye et al., 2006) and Madagascar (Fontenille et al., 1990). *An. arabiensis* have been experimentally infected with *P. vivax* from infected monkeys (Collins et al., 2009).
An. funestus Giles	Yes	Yes	*P. vivax* (VK247) circumsporozoite proteins were found in *An. funestus s.s.* specimens collected in Kenya (Ryan et al., 2006).

Continued

Table 1.2 Known and potential vector species of *Plasmodium vivax*—cont'd

Species, species complex* or group	Distribution and bionomics reviewed by MAP†	*P. vivax* vector (Yes/No)‡	Notes and reference(s)
An. gambiae Giles/ *An. gambiae* complex	Yes	Yes	*P. vivax* (VK247) circumsporozoite proteins were found in *An. gambiae s.s.* specimens collected in Kenya (Ryan et al., 2006) and *An. gambiae* has been infected with *P. vivax* in laboratory settings from infected monkeys (Wirtz et al., 1985; Collins et al., 2009).
An. labranchiae Falleroni	Yes	Yes	*An. labranchiae* has been stated to be a vector of *P. vivax* (Lindsay and Thomas, 2001; Romi et al., 2001), and a vectorial capacity for *P. vivax* in *An. labranchiae* has been estimated (Romi et al., 1997; Romi et al., 2001).
An. melas Theobald	Yes (part of the *An. gambiae* complex)	?	No natural *P. vivax* infection has been found (Moreno et al., 2004; Bigoga et al., 2007), but that is perhaps because the indigenous populations, rather than the mosquito, are refractory to *P. vivax* (Moreno et al., 2004).
An. merus Dönitz	Yes (part of the *An. gambiae* complex)	?	No natural *P. vivax* infection has been found; *An. melas* sampled in Tanzania were found not to be infected with *P. vivax* (Temu et al., 1998).
An. moucheti Evans	Yes	?	There is no indication of *P. vivax* infection, but this may be due to lack of the parasite within its distribution (Antonio-Nkondjio et al., 2005).
An. multicolor Cambouliu	No	Yes(?)	No *P. vivax* parasites were found in *An. multicolor* collected in desert oases in Egypt (El Said et al., 1983; Kenawy et al., 1990; Morsy et al., 1995). However, the authors infer the potential for transmission and refer to experimental transmission of *P. vivax* by *An. multicolour* under laboratory conditions.

An. nili complex	Yes	?	There is no indication of *P. vivax* infection by ELISA in specimens sampled in Ethiopia (Nigatu et al., 1994), but this may be due to lack of the parasite within its distribution (Antonio–Nkondjio et al., 2005).
An. pharoensis Theobald	No	Yes	*P. vivax* circumsporozoite proteins were detected by ELISA in *An. pharoensis* sampled in southwest Ethiopia (Nigatu et al., 1994).

Vector species were identified during the preparation for a series of articles (Hay et al., 2010c; Sinka et al., 2010a, 2010b, 2011, 2012) regarding the dominant vector species of human malaria. The potential for 71 anopheline species and species complexes to transmit *P. vivax* are shown alphabetically by region.
*Harbach (2004).
†Sinka et al. (2010a, 2010b, 2011, 2012).
‡Yes = evidence of wild/naturally infected mosquitoes; Yes(?) = evidence of laboratory infected mosquitoes or secondary information implicating species as a vector; ? = no information found to confirm species can carry *P. vivax*, but nothing to state it cannot, or unconfirmed or unclear references to species *P. vivax* vector status.

(Sinka et al., 2012). In addition to its sympatric range with *An. culicifacies s.l.* and *An. fluviatilis s.l.* over India, *An. stephensi* was predicted to occur in Afghanistan and Pakistan, where it was sympatric with *An. superpictus*.

The sources for the following summary can be found in Sinka et al. (2011) and Sinka et al. (2010a).

The DVS cover a large range of varying ecological niches and the presence of a large number of species complexes in the region means that variation in behaviours are often seen. Indeed, behavioural variability within a species is also common, for example, *Anopheles annularis* has a range extending across India, down through South-East Asia, across many of the Indonesian islands and Timor Island. However, *An. annularis* only has a focal role in malaria transmission in selected areas of India. Elsewhere it is considered of little importance.

The Indian DVS have overlapping, sympatric ranges and include a number of species complexes. For example, there are five sibling species in the *An. culicifacies* complex (species A, B, C, D and E) and although species A, C, D and E are all reported to be vectors of malaria in India (Sinka et al., 2011), species E is the most important because of its highly anthropophilic and endophilic behaviour. Members of the complex are found across the plains and up into the highlands (Iyengar, 1954; Barik et al., 2009). Larval habitats include a variety of man–made and naturally occurring water bodies and tolerance of brackish water has been observed in species E (Roberts, 1996). Species C shows plasticity in its behaviour, being found in both forested and deforested areas. Varied bionomics are therefore observed both within and among members of this species complex.

The other primary Indian DVS are *An. fluviatilis s.l.* and *An. stephensi*. Variable behaviour is observed amongst the three members of the Fluviatilis Complex (species S, T and U). Within the complex, there are reports of anthropophilic, zoophilic and exo- and endophagic populations, biting at dusk and during the night. *Anopheles stephensi* is primarily zoophilic and endophagic, and both *An. fluviatilis s.l.* and *An. stephensi* rest primarily indoors. *Anopheles stephensi* is unusual amongst *Anopheles* species in that it appears to be able to use virtually any water condition/habitat as a larval site, hence, its success in urban areas. Less is known regarding the larval habitats of *An. fluviatilis s.l.*, but the complex is associated with slow–moving streams or river margins.

Amongst the northern Asia DVS, *An. sinensis s.l.* and *An. superpictus* are considered potential primary vectors of *P. vivax*. In Thailand, members of the *An. sinensis* complex are considered zoophilic and exophagic, and therefore,

of little vectorial importance. In the Korean Peninsula, on the other hand, *An. sinensis s.l.* shows a propensity for biting humans and has been identified as a primary vector (Lee et al., 2001). The larvae of *An. sinensis* complex are associated with lowland, shallow, freshwater habitats. Adult females may hibernate to overwinter from October to April when the temperatures drop below 19 °C (Chow, 1970). Little is known regarding the biting habits of *An. superpictus*, particularly regarding host preference, but they are generally considered to be exophagic. The larvae are commonly found in shallow, flowing, fresh, sun-lit water. However, the species can adapt to human influences by using man-made pits and holes.

The primary DVS in the south-eastern part of Asia are the *An. dirus* and *An. minimus* complexes, both of which contain highly competent vector species. Within the Dirus Complex, which contains seven sibling species, again there is some variability in behaviours (depending on location and sibling species) but the main vectors of the complex (*An. dirus s.s.* and *Anopheles baimaii*) are both highly anthropophilic and will feed both indoors and out. Biting activity appears highly sibling/species dependent with *Anopheles scanloni* (a focal vector within the complex) biting at dusk, *An. dirus* biting in the evening (between 2000 h and 2300 h) and *An. baimaii* biting as late as 0200 h. In general, outdoor resting both before and after feeding has been reported for this species complex. The larvae of this complex inhabit small, temporary, freshwater bodies and are therefore most abundant during the rainy (monsoon) season. *Anopheles minimus s.l.* has three siblings, only two of which (*An. minimus s.s.* and *Anopheles harrisoni*) are considered viable contemporary vectors. Variability in reported behaviour may be a consequence of misidentification or lack of differentiation between these two species, although both are also considered opportunistic and plastic in their behaviour. *Anopheles minimus s.s.* is potentially more anthropophilic, but also adaptable depending on host availability. Overall, *An. harrisoni* is considered more exophagic, exophilic and zoophilic than its sibling. Minimus Complex larvae are typically associated with small- or moderate-sized streams with slow, clear, cool and partially shaded water. *Anopheles minimus s.s.* has been observed in a wider range of habitats from canopied forests to open fields. *Anopheles harrisoni*, on the other hand, is more commonly associated with agricultural areas. Further studies that utilise molecular assays to differentiate sibling species are needed to understand the varied behaviour and habitat preference of *An. minimus s.s.* and *An. harrisoni*.

It is clear that the behaviour of the Asian vectors is complicated, variable and, as yet, not well understood. However, many of the species do exhibit

characters that are amenable to control, for example, those that bite indoors at night are conducive to control using ITNs and indoor resting facilitates the effectiveness of IRS.

Asia summary. *Plasmodium vivax* is an important public health problem across large parts of Asia. Six of the 10 largest PAR estimates of the 95 *Pv*MECs were in Asia and these countries accounted for 87% of the global PAR. Control of *P. vivax* in *Pv*MECs in Asia would, therefore, dramatically reduce the impact of this widespread disease. In Asia, in particular, densely populated areas are endemic with stable *P. vivax* transmission. This is due to environmental suitability as well as a vector species (*An. stephensi*) that is well suited to urban transmission. The limits and endemicity maps produced show that *P. vivax* has a wide geographic range in this region, across which the level of transmission is generally low, with small pockets of intense stable transmission (Fig. 1.3A1 and A2). In high-prevalence areas, such as those found in parts of India (Orissa State) and Myanmar, the clinical character of *P. vivax* has been found to behave more like *P. falciparum*, resulting in cases of severe disease and death (Mendis et al., 2001; Baird, 2007; Price et al., 2007a; Kochar et al., 2009; Mahgoub et al., 2012). Uncertainty estimates were high throughout India and much of Myanmar and population-weighted esti- mates emphasise the need to improve the estimates in India with more sur- vey data (Fig. 1.4A1 and A2). Improved *P. vivax* surveillance in these regions would greatly improve prevalence predictions. By 2012, several countries in this region (Azerbaijan, Bhutan, China, Georgia, Korea DPR, Republic of Korea, Kyrgyzstan, Sri Lanka, Tajikistan, Thailand, Turkey, Uzbekistan and Viet Nam) had entered the malaria elimination phase (The Global Health Group and the Malaria Atlas Project, 2011). Improved control in neigh- bouring countries with intense, stable transmission, such as Myanmar, will improve the success of those nations already working towards elimination by reducing the potential for imported malaria from human migration (Tatem and Smith, 2010). As elimination efforts continue, spatially detailed mapping will be needed to capture focal areas of transmission that remain. Further and improved vector surveillance using molecular techniques to disaggregate species complexes is needed to illuminate which vectors are truly the primary vector species of *P. vivax* to allow for appropriate control measures to be deployed in this highly variable region.

4.2. Asia-Pacific

The Asia–Pacific region (defined for these purposes as the southern islands of Asia–Pacific and the Malaysian Peninsula; Fig. 1.2) has amongst the highest

endemicity estimates of *P. vivax* malaria (Fig. 1.3B) and the most complex spectrum of vectors. This region has a relatively small land mass, which means it has a much lower estimated PAR but the range in epidemiological and entomological factors here mean it presents a unique and challenging control setting.

Defining the limits of transmission. Annual parasite index data were provided for all the *P. vivax*-endemic countries in Asia–Pacific. The *Pv*MECs in this region are Indonesia, Malaysia, the Philippines, Papua New Guinea, the Solomon Islands, Timor-Leste and Vanuatu.

Transmission was estimated to span 2.74 million km^2 of land in this region, which is primarily made up of islands. The area at risk in Asia–Pacific constituted 6% of the global area at risk. Indonesia, the largest country in the region, had the greatest area at risk, consisting of 1.71 million km^2 of land, which was 90% of the country's total area (1.90 million km^2) and 60% of the total area at risk for the region.

Estimating endemicity. There were 5277 records of prevalence data collected from Asia–Pacific, which made up more than half (53%) of the global *P. vivax* PR survey database. This was primarily due to a large data contribution from Indonesia, which provided 4457 (84%) data points in the Asia–Pacific region and 45% of the global dataset (Fig. 1.3B1).

As with mainland Asia, *P. vivax* endemicity in regions with stable transmission was predicted to vary greatly across the Asia–Pacific region as shown in Panel B2 of Fig. 1.3. PvPR$_{1-99}$ point estimates were predicted to exceed 7% in small parts of Indonesia and the Solomon Islands, and much of Papua New Guinea. Estimates towards the east of the region (Sumatra and Kalimantan) were generally low, while endemicity values of around 5% were predicted to the north (Malaysian Borneo and the Philippines). The vast number of surveys from Indonesia meant that the certainty of the predictions in that portion of the region was relatively high (Fig. 1.4B1). Uncertainty was greatest on New Guinea and parts of Borneo, where prevalence data were sparse. The Philippines, which also had little survey data available, was predicted with relatively low certainty. Again, the population-weighted uncertainty map was substantively different (Fig. 1.4B2). While the highly populated areas of Asia were predicted with less certainty, the high-density areas of Asia–Pacific, which also had a high number of prevalence surveys (Indonesia), showed an increase in certainty in the population-weighted estimates. Uncertainty was also greatly reduced following population-weighting in focal areas in Papua, Indonesia and Papua New Guinea, where population density is low. The Philippines had relatively low uncertainty

even when weighted by population estimates, indicating that this region would benefit from increased prevalence surveillance data.

Population at risk. Relative to the geographic size of the region, Asia–Pacific had a large PAR due to pockets of intense transmission in highly populated endemic areas. It was estimated that there were 215 million people at risk in this region. This was only 11% of the PAR in mainland Asia. However, the proportion of the population that was at any risk of *P. vivax* relative to the total population of the *Pv*MECs in Asia–Pacific was comparable to the Asia region: the PAR was 59% of the total population in Asia–Pacific and 58% in Asia. The largest PAR in Asia–Pacific was in Indonesia, with an estimated population of 129.28 million individuals at risk of *P. vivax* out of a total population of 231.60 million (56%) in 2010. The PAR of stable and unstable transmission in Indonesia was 60% of the PAR of Asia–Pacific as a whole. The next largest PAR estimates were from the Philippines and Malaysia. The Philippines had 50.34 million people at risk or 54% of the total population of the Philippines and 23% of the regional PAR. Malaysia had 27.88 million (99.8% of the Malaysian population; 13% of the regional PAR) people at risk. Papua New Guinea had a PAR of 5.64 million (81% of the national population; 3% of the regional PAR) and Timor–Leste had 1.15 million (98% of the national population; 0.5% of the regional PAR). The Solomon Islands and Vanuatu had a PAR less than one million: 0.53 and 0.24 million (both nearly 100% of the total national populations and <0.3% of the regional PAR). Seventy percent of the total PAR in the region was exposed to unstable transmission. Unstable transmission predominated in Indonesia and Malaysia, where 79% (26.78 million) and 84% (4.45 million) of the PAR, respectively, were exposed to that level of transmission. In the Philippines, 53% (26.59 million) of the PAR lived in areas of stable transmission. Nearly all of the transmission in Vanuatu was stable (99.57%). The entire PAR in both Timor–Leste and the Solomon Islands experienced stable transmission. More than half of the population (59%) in Asia–Pacific is at risk of some level of vivax malaria transmission and the 215 million people at risk was 8.7% of the global PAR.

Vectors. Of the 26 potential vector species of *P. vivax* (Table 1.2), we predict that 16 are DVS that occur in Asia–Pacific (*Anopheles aconitus*, *An. annularis*, *An. balabacensis*, *An. barbirostris* complex, *An. dirus* complex, *An. farauti* complex, *An. flavirostris*, *An. koliensis*, *An. lesteri*, *An. leucosphyrus* & *An. latens* (sister species grouped together here due to known mis–identification problems within the current literature), Maculatus Group, *An. minimus* complex, *An. punctulatus* complex, *An. sinensis* complex, *An. subpictus* complex

and *An. sundaicus* complex), six of which are found only in Asia–Pacific (*An. balabacensis*, *An. farauti* complex, *An. flavirostris*, *An. koliensis*, *An. leucosphyrus* & *An. latens*, and the Punctulatus Group) (Sinka et al., 2011). The predicted distributions of the DVS in this region are shown in Fig. 1.9B.

For the 16 Asia–Pacific DVS, 9052 unique georeferenced occurrence records were assembled. The most data-rich species/species complexes were the *An. farauti* (*n* = 1737), *An. subpictus* (*n* = 1143) and *An. barbirostris* (*n* = 1064) complexes; and the most data-poor were *An. leucosphyrus* & *An. latens* (*n* = 12). Occurrence data were reported from all seven *Pv*MECs in this region. Most of the data originated from Papua New Guinea (*n* = 1503 sites), followed by Indonesia (*n* = 890), Solomon Islands (*n* = 160), Malaysia (*n* = 145), the Philippines (*n* = 124), Vanuatu (*n* = 36) and Timor-Leste (*n* = 1). Given the heterogeneity in vector distribution in this region, improved data collection from many of these countries would improve the fidelity of the predicted distributions of this complicated region.

The distribution and behaviour of the DVS discussed below are those that met the criteria for having broad distributions in the region (Fig. 1.9C) and have been conclusively incriminated as vectors of *P. vivax* (Table 1.2). A complete discussion of their ranges and bionomics may be found elsewhere (Sinka et al., 2011, 2012). The species that were identified as specific vectors of *P. vivax* in Asia–Pacific are *An. barbirostris s.l.*, *An. farauti s.l.*, *An. koliensis*, *An. leucosphyrus* & *An. latens* and *An. punctulatus s. l.*

Anopheles barbirostris s.l. is predicted to occur across large areas of inland Sumatra and Borneo. It is typically a highland species, but is also found in coastal regions (e.g. western Timor). Adult females of this species complex tend to feed outdoors on animals during dusk and night time, bringing its significance as a vector of malaria into question. Further molecular analysis and identification of the sibling species is needed to determine if variations observed in biting behaviours are due to plasticity within a species or differences amongst different species in the complex. A variety of larval habitats are also observed for *An. barbirostris s.l.* Though they are typically considered swamp breeds, a variety of water depth, size, light intensity and movement has been observed. This variation may again be due to the differences among species within the complex rather than the plasticity of a single species.

Anopheles farauti s.l., *An. koliensis*, and *An. punctulatus s.l.* are in sympatry across most of the islands of New Guinea, New Britain and into the Solomon Islands. All three are found within the Punctulatus Group. There are two sibling species in the Punctulatus Complex: *An. punctulatus s.s.* and *Anopheles* sp. near *punctulatus*.

The latter of the two species is relatively uncommon, whereas *An. punctulatus s.s.* is reportedly widespread and an important vector on the island of New Guinea. The distribution of *An. punctulatus s.s.* spans eastern Indonesia, Papua New Guinea and the Solomon Islands. Adult females feed readily on humans outdoors or occasionally indoors. Those that feed indoors may rest there, but are more likely to exit to find an outdoor resting spot. Peak biting times vary based on the geographic location. The larvae of *An. punctulatus s.s.* thrive in temporary pools that result from disturbed ecology. The habitats tend to be small, shallow, sunlit pools of water that may be turbid, but never brackish.

The distribution of the eight cryptic species of the Farauti Complex is largely dependent on the species' tolerance of salinity such that some members are coastal species (e.g. *An. farauti s.s.*) while others are restricted to inland areas with freshwater larval habitats (e.g. *Anopheles hinesorum*). The feeding habits of *An. farauti s.l.* also vary; host preference changes based on the availability of hosts and resting may be dependent on where feeding occurred. Peak biting times fluctuate with location, but it should be noted that daytime biting may occur. The larval habitats of members of the complex are typically in natural rain–fed water bodies, but artificial containers such as water drums or coconut shells may also be used. The habitats range in salinity and light intensity due to the wide geographic distribution of the species complex.

The predicted distribution of *An. koliensis* is similar to that of the Punctulatus Complex. The adult females tend to be anthropophilic, but will feed on other animal hosts. Although females may go indoors in search of a host, resting typically occurs outdoors. Feeding can occur throughout the night, with variable peak times based on location. The larval habitats of *An. koliensis* are intermediate between those of *An. farauti s.l.* and *An. punctulatus s.l.* and are generally associated with permanent freshwater bodies in open grassland such as irrigation ditches.

Anopheles leucosphyrus and *An. latens* are sister species of the Leucosphyrus Complex. Both species are found in forested areas with the former on the island of Sumatra and the latter on the southern portions of the Thai and Malaysian Peninsula and parts of Borneo. Both species are considered to be important vectors of malaria and were long thought of as the same species until molecular and cross–mating studies distinguished between them (Baimai *et al.*, 1988). Little is known of the bionomics of *An. leucosphyrus s.s.* because much of the literature on '*An. leucosphyrus*' is now known to refer to *An. latens*. The species has been shown to bite humans both inside and outside, however. *Anopheles latens* bites throughout the night with peak

times that vary based on the seasonal climate and location. Its larval habitats include shaded temporary pools found in the forest such as swamps, stump ground holes or wheel tracks.

The bionomics of the DVS in Asia–Pacific are as variable as in mainland Asia. This is due to variation observed both within species complexes and among separate species. Such variations increase the challenge of developing a single universal vector control strategy across the region, however, a combination of methods could prove effective (Lindsay et al., 2004).

Asia-Pacific summary. The vivax malaria problem in Asia-Pacific is complex and presents a variety of challenges to control. Indonesia and the Philippines are densely populated over large land masses (Fig. 1.8B) and *P. vivax* is predicted to be endemic across most of their national territories. They have the fourth and fifth largest PAR estimates globally with 129 million at risk in Indonesia and 50 million in the Philippines. Some of the highest predicted $PvPR_{1-99}$ values were also observed in this region (Fig. 1.3B1). As in the Asia regions, it is in these areas, where intense *P. vivax* transmission occurs (e.g. Indonesia and Papua New Guinea), where drug resistance is emerging and malaria cases of equivalent clinical severity to *P. falciparum* have been observed (Baird, 2004; Pukrittayakamee et al., 2004; Tjitra et al., 2008; Price et al., 2009). This and the large areas of unstable transmission make this region a worthy and vital candidate for research, control and eventually elimination efforts; four of the seven *Pv*MECs have already declared their status of working towards elimination: Malaysia, the Philippines, the Solomon Islands and Vanuatu (The Global Health Group and the Malaria Atlas Project, 2011). Uncertainty estimates, shown in Fig. 1.4B1 and B2, were high in areas that also displayed high $PvPR_{1-99}$ estimates (Fig. 1.3B2), such as Papua New Guinea. While the population-weighted correction shows that parts of these regions are, for the most part, sparsely populated (Fig. 1.8B), improved surveillance to facilitate high-resolution mapping will be essential to tackle the final transmission hotspots of this region as elimination efforts progress. The vector situation in this region is complex and further research is needed to differentiate members of species complexes and incriminate those vectors that are vectors of *P. vivax* so that appropriate control measures may be taken.

4.3. Americas

The Americas have amongst the highest *P. vivax* endemicity values in the world but these typically occur in areas of very low population density, so the populations at risk are much lower than those found in Asia (Fig. 1.3C1 and Fig. 1.8C). The diversity of vector species is also less in this region (Fig. 1.9C).

Defining the limits of transmission. *Plasmodium vivax* annual clinical incidence data were available from all 19 countries that are considered to be endemic in the Americas. The most recent year of reporting was 2008 for the majority of the countries. Guyana, Nicaragua and Panama reported data up to 2007; Belize, El Salvador, French Guiana and Guatemala provided data up to 2006 and Colombia's last year of reporting was 2005.

Endemic areas in this region were estimated to span 9.46 million km^2, most of which were found in the Amazon basin. The majority of the areas at risk in the Americas (85%; 8.08 million km^2) were at stable transmission (Fig. 1.3C1). This indicated that, for the most part, the disease was either endemic or wholly absent in this region with limited areas at risk of unstable transmission. The transmission level was generally found to be inversely proportional to the population density: areas experiencing stable transmission were those of lower population density. For example, the largest area at risk of stable transmission in a single country was 4.40 million km^2 in Brazil, which was 54% of the stable transmission area for the Americas region. However, the population at stable risk in Brazil was 26% (13.02 million) of the region's total PAR of stable transmission. The Americas comprised 53% of the global land area at stable transmission but only 5% of the population at that level of risk.

Estimating endemicity. There were relatively few PR records and surveys for the Americas, with 388 unique records available for modelling. The three most data-rich countries in this region were Brazil ($n = 175$; 45%), Venezuela ($n = 65$; 17%) and Peru ($n = 51$; 13%), as shown in Fig. 1.3C1.

The predicted prevalence, or PvPR$_{1-99}$, was highly variable throughout the Americas. Much of the areas of stable transmission had PRs between 3 and 5%, with isolated areas nearing 0% and others exceeding 7%. Regions of high prevalence (>7%) were found in Amazonia (Northeast Brazil) and Central America (Nicaragua and Honduras). The uncertainty in the PvPR$_{1-99}$ predictions was relatively high overall due to the relatively sparse PR survey data in this region (Fig. 1.4C1). However, when population density was incorporated into the weighted uncertainty calculations, the resulting uncertainty index was greatly lowered because the areas with stable risk and high uncertainty predictions had low population densities (Fig. 1.4C2). This implies that the observed uncertainty has relatively little operational importance at the global scale, although highlights the current lack of precision for defining high-risk foci in remote Amazonian settings.

Population at risk. The PAR in the Americas was relatively low given the geographic limits of *P. vivax* due to low population densities in areas of high transmission. It was estimated that there were 137.45 million people living

at risk of *P. vivax* in the Americas in 2010. The majority of the PAR was in areas of unstable transmission (64%; 87.66 million) and 36% (49.79 million) were exposed to stable *P. vivax* transmission. Brazil had the largest PAR with 45.22 million people living at any risk, which is 26% of its total population and represents 33% of the region's PAR). The largest number of people living at stable risk (13.02 million) was in Brazil, followed by Venezuela with 4.43 million at stable risk and 22.87 million total at risk (83% of the national population and 17% of the regional PAR). Colombia was estimated to have 7.53 million at stable risk and 19.15 million at risk (56% of its total population and 14% of the region's total). El Salvador, with a PAR 3.17 million, did not have any individuals living at stable risk. French Guiana (PAR 158,000) and Suriname (PAR 30,000; the lowest PAR in the region) did not have any populations living at unstable risk. The portion of the PAR at stable transmission in Belize was also nearly 100%; only 30 individuals out of 220,000 at risk were in unstable transmission areas. Of the 1.5 billion people living at unstable and 964 million at stable transmission around the globe, 5.8% and 5.2% of those were found in the Americas, respectively.

Vectors. Of the 20 potential vectors (Table 1.2) of *P. vivax* in the Americas, nine are considered DVS. These include *Anopheles albimanus*, *An. albitarsis* complex, *An. aquasalis*, *An. darlingi*, *An. freeborni*, *An. marajoara*, *An. nuneztovari* complex, *An. pseudopunctipennis* and *An. quadrimaculatus* (Sinka et al., 2010b). The predicted distribution of these species is shown in Fig. 1.9D. There were 4141 georeferenced spatiotemporally unique occurrence points obtained for *Anopheles* DVS from 25 countries in the Americas. Twenty-two percent of the occurrence records ($n = 926$) referred to *An. darlingi* and 20% ($n = 851$) to *An. albimanus*. The remaining species had occurrence data of between 63 (*An. freeborni*) and 572 (*An. quadrimaculatus s.l.*) records. Of the total number of point locations identified ($n = 1509$), the greatest number came from the United States ($n = 377$), followed by Brazil ($n = 304$) and Belize ($n = 228$). The *Pv*MECs with the fewest point records (<10) were French Guiana ($n = 7$), El Salvador ($n = 3$), Paraguay ($n = 2$), Guyana ($n = 1$), Honduras ($n = 1$) and Nicaragua ($n = 1$).

Distribution maps indicate a relatively straightforward vector profile across the *Pv*MECs of the Americas. Of the nine DVS in this region, *An. darlingi* and *An. albitarsis s.l.* met the criteria for further description because these species are predicted to have a wide distribution in the region and conclusive supporting evidence indicating transmission of *P. vivax* in the wild, indeed, the distribution of *An. darlingi* is remarkably similar to that of *P. vivax* in the region (1.3C2 and 1.9D). Although *An. darlingi* is considered

a riverine species inhabiting forest locations, it has been observed to take advantage of deforestation, exploiting areas with reduced canopy cover compared to those more densely forested locations. The larval habitats of this species are typically clear and natural water bodies such as slow-flowing, clear rivers and streams. Adult female *An. darlingi* are both exo- and endophagic, though they tend to rest outdoors regardless of where their blood meal was taken. Host preference also varies within this species as does biting activity (time of biting), which may adapt to correspond to human behaviour (i.e. late night human activity influences or causes late night biting by *An. darlingi*).

The Albitarsis Complex is composed of five sibling species including the known vectors, *An. albitarsis*, *An. deaneorum* and *An. marajoara*. Members of this complex exhibit some behaviours that are similar to *An. darlingi*, for example, the adult females tend to rest indoors but will bite indiscriminately without much host preference both indoors and outdoors. The larval habitats tend to be clear, sunlit, freshwater.

The Americas summary. National surveillance data have shown a widespread decrease in morbidity and mortality from both major *Plasmodium* species across the American continent since 2000 (WHO/PAHO, 2008). This is due largely to the successful implementation of integrated vector management (Roberts et al., 1997; Butler and Roberts, 2000; Rojas et al., 2001; Killeen et al., 2002; Roberts et al., 2002; Shiff, 2002; WHO/PAHO, 2006) and has led eight of the 21 *Pv*MECs in the Americas (Argentina, Belize, Costa Rica, El Salvador, Mexico, Nicaragua, Panama and Paraguay) to target malaria elimination (The Global Health Group and the Malaria Atlas Project, 2011). However, the prevalence estimates of *P. vivax* in the Americas are heterogeneous with isolated areas of intense transmission (Fig. 1.3C2). Vector occurrence data coverage was uniformly low in the American *Pv*MECs. Improved vector research in the Americas will advance the maps of species-specific distributions, which is essential for the continued success of vector management to curb malaria morbidity and mortality. Pockets of high transmission (*Pv*PR > 7%) were observed in large areas of the region. However, it is important to note that these were generally in areas with low population estimates. Sparse prevalence data resulted in high uncertainty estimates in the region that were greatly reduced when the density of the population in endemic areas was taken into consideration (Fig. 1.4C). *Anopheles darlingi* appears to be the primary vector in this region; however, eight of the potential vectors of *P. vivax* in this region lack conclusive evidence regarding their potential to transmit the parasite. Therefore, further research is needed to decisively incriminate the vectors of *P. vivax* in the Americas.

Plasmodium vivax makes up the vast majority of malaria transmission that occurs in the Americas (Arevalo-Herrera et al., 2010). Survey data from this region were relatively sparse and records represent a picture of heterogeneous transmission levels. The Americas contributed a small fraction (5.5%) of global PAR of *P. vivax*, but comprised nearly a quarter (22%) of the global area at risk. Areas of high transmission in highly dispersed populations may present unique challenges to malaria control. To advance elimination efforts, high-resolution mapping will be needed to accurately illustrate the degree of heterogeneity in this region and areas that require the greatest resources. This will demand more data from areas with high predicted prevalence and uncertainty, such as Honduras and Nicaragua in Central America and northwest Brazil in South America. Although Brazil is a large and populous country, its areas of stable transmission occur in sparsely populated regions of the Amazon basin. In 2010, Brazil had the seventh largest PAR of *P. vivax* globally (45 million), the largest area at risk (4.90 million km^2) as well as the largest area at stable risk (4.40 million km^2) and, therefore, has an important role to play in the region's future of malaria control and elimination.

4.4. Africa+

The estimates for endemicity and populations at risk of *P. vivax* malaria in Africa+ (defined here as Africa, Saudi Arabia and Yemen) are mitigated by the high prevalence of Duffy negativity in these populations, and the vector situation in this region is relatively straightforward.

Defining the limits of transmission. High *P. falciparum* endemicity in Africa, coupled with high prevalences of Duffy negativity, has meant that collection of *P. vivax*–specific data has not been a priority in the past. The data available from which to estimate the limits of *P. vivax* transmission is, therefore, limited. *Plasmodium vivax* annual parasite incidence (*Pv*API) data were only available from six Africa+ countries (13%). The last year of reporting available was 2009 for four countries (Dijbouti, Namibia, South Africa and Swaziland); whilst for the remaining two countries (Saudi Arabia and Yemen) the last available reports were from 2006. Based on the limited *Pv*API and *Pv*PR data available for Africa+, and the presence of suitable vectors and climatic conditions, forty-six countries are assumed to be *P. vivax* endemic in this region.

The area at risk was estimated to span over 22 million km^2 of Africa, Yemen and Saudi Arabia. Despite the historical misconception that *P. vivax* is absent from the African continent, 84% of the 22.46 million km^2 of land in the region was at some risk of *P. vivax* transmission (Fig. 1.3D2). However, the vast majority (92%; 20.60 million km^2) of total area at risk was estimated to house unstable transmission.

Estimating endemicity. There were 1640 records of prevalence data from 97 sources obtained for Africa+, 79% of which reported an absence of *P. vivax*. Approximately 16% of the global *Pv*PR data records used in the modelling were from surveys conducted in Africa, Yemen and Saudi Arabia. Ethiopia, Zambia and Sudan were the most data rich countries, contributing 50% ($n = 826$), 18% ($n = 295$) and 18% ($n = 290$) of the total data, respectively.

The predicted prevalence estimates were uniformly low for areas at stable risk in Africa, Yemen and Saudi Arabia as shown in Fig. 1.3D2. The point estimates of predicted PvPR$_{1-99}$ rarely exceeded 2%. The uncertainty of the predictions in this region was also very low (Fig. 1.4D). The incorporation of information regarding the proportion of Duffy negative individuals strengthened the predictions in this area and compensated for the sparse parasite rate data available from this region (Fig. 1.3D1, Fig. 1.4D and Fig. 1.7D). Areas with higher PvPR$_{1-99}$ (Ethiopia, South Sudan and Madagascar) predictions were also found to have the highest uncertainty, likely because these areas were outside the range of high Duffy negativity and could not borrow from the certainty conferred by that restriction. As with the Americas, the uncertainty in Africa+ was reduced in the population-weighted predictions because of the low population density found in parts of the continent, particularly Madagascar (Fig. 1.4D2). Uncertainty remained relatively high in the highlands of Ethiopia, which are more densely populated and are therefore important targets for control.

Population at risk. The PAR in Africa+ was low given the large geographic coverage of the region because of the high prevalence of Duffy negativity (Fig. 1.3D1 and Fig. 1.7D). There were an estimated 86 million people living at risk of *P. vivax* in Africa, Yemen and Saudi Arabia in 2010, which was 3.5% of the global total. More than half (56%), or 48.72 million, of the PAR were those living in unstable transmission and the remaining 37.66 million (44%) lived in areas at the level of stable transmission. Nine countries had an estimated PAR of zero, all of which are located in West Africa: Côte d'Ivoire, Ghana, Guinea, The Gambia, Guinea-Bissau, Senegal, Sierra Leone and São Tomé and Príncipe. Togo, Equatorial Guinea, Gabon and Burkina Faso also had a total PAR of less than one thousand individuals. Thirty-four countries in the Africa+ region had zero individuals at risk of stable transmission. Of the 12 countries with stable transmission, Madagascar was the only country where the entire PAR (5.23 million) experienced stable transmission. Madagascar has the fourth highest PAR in the region; the highest were Ethiopia, Sudan and Yemen with 35.19 million (41% of

the PAR in the Africa+ region), 14.78 million (17%) and 13.06 million (15%) people at risk in each, respectively.

Although the high proportion of Duffy-negative individuals in Africa is thought to result in an absence of the parasite across the continent, evidence of transmission in Africa+ (Guerra et al., 2010; Ménard et al., 2010) supported the decision to assume stable transmission in all areas of Africa+ that were not excluded by *Pv*API data or biological masks. Areas were then reclassified following *Pv*PR$_{1-99}$ predictions such that locations with endemicity levels below 1% were reclassified as unstable; this was the majority of the region. High proportions of Duffy negativity are especially common among the population of West Africa. Ghana, for example, had a PAR of 24 million individuals when accounting for environmental exclusions and before the inclusion of Duffy negativity, which subsequently reduced the PAR of Ghana to zero. The incorporation of the Duffy negativity layer reduced the PAR of the Africa+ region from 840 million to 86 million, which is 3.5% of the global PAR of *P. vivax*.

Vectors. The high impact of malaria on the African continent is largely due to the efficiency of the African DVS in transmitting *P. falciparum*. However, *P. vivax* may also play an important role. As more countries on the continent move towards elimination, there may be in shift in the endemicity of *P. vivax* as levels of *P. falciparum* decline. It is essential to know which vector species are capable of transmitting *P. vivax*.

Africa is the home to two of the most efficient vector species of human malaria: *An. gambiae* and *An. funestus* (Gillies and de Meillon, 1968; Coluzzi, 1999). Of the 10 potential vectors of *P. vivax* in Africa+ (Table 1.2), eight (*Anopheles arabiensis*, *An. funestus* complex, *An. gambiae* complex, *An. Labranchiae*, *An. melas*, *An. merus*, *An. moucheti* and *An. nili* complex (Sinka et al., 2010a)) are considered to be DVS of human malaria, but their importance in transmitting *P. vivax* is still uncertain. For example, it is unclear whether the forest vector *An. moucheti* is a poor/non-vector of *P. vivax* or that this parasite simply does not exist in areas where this species occurs (Table 1.2). The distributions of *An. arabiensis*, *An. funestus s.l.* and *An. gambiae s.l.* and the DVS that occur in Saudi Arabia and Yemen are shown in Fig. 1.9E. Only the three primary DVS are shown in Africa because of the lack of evidence of the ability for the other African DVS to transmit *P. vivax* (Table 1.2). For the African DVS there were 8338 spatially and temporally unique occurrence records. The majority of these occurrence records were obtained for *An. funestus s.l.* (*n* = 2692), *An. arabiensis* (*n* = 2301) and *An. gambiae s.l.* (*n* = 2291). Point data were obtained from 44 countries. The largest number

of point records per country were from Kenya ($n = 757$), followed by Tanzania and Cameroon ($n = 383$ for both nations). For the most part, the other countries on the continent had less than 100 point records, with the exception of Burkina Faso ($n = 310$), Equatorial Guinea ($n = 113$), Ghana ($n = 106$), Madagascar ($n = 198$), Mali ($n = 166$), Nigeria ($n = 190$), Senegal ($n = 209$), Sudan ($n = 125$), the Gambia ($n = 192$) and Uganda ($n = 135$). African countries classified as *P. vivax* endemic that had very few (≤5) vector occurrence point records were Central African Republic ($n = 3$), Congo ($n = 2$), Liberia ($n = 4$), Namibia ($n = 5$) and Togo ($n = 1$).

The compiled species distribution maps (Fig. 1.9E) illustrate a relatively straightforward picture of the distribution of the region's DVS: *Anopheles arabiensis*, *An. funestus s.l.*, and *An. gambiae s.l.* which all have broad distributions in the region and are confirmed vectors of *P. vivax*. These three DVS dominate in heterogeneous ranges of different pairs and combinations (of one another) in such a way that the species are present on their own in only focused locations. The co-dominant range of the *An. funestus* complex and *An. gambiae* in Central Africa is surrounded by an 'envelope' that houses all three primary DVS, that is further surrounded by *An. arabiensis* and the Funestus Complex, and then only *An. arabiensis* on the periphery. *Anopheles arabiensis* tolerates drier environments and is therefore absent from the forested areas of western Central Africa. The *An. funestus* complex distribution indicates a presence throughout all of sub-Saharan Africa, including Madagascar, but excluding much of southern Africa. *Anopheles gambiae* has a more complex distribution across a band from East (including Madagascar) to West Africa.

The bionomics of all the African DVS of malaria are summarised in full elsewhere (Sinka et al., 2010a). Here, we briefly describe the behaviours of those three DVS identified as potential *P. vivax* vectors in the region. *Anopheles arabiensis*, *An. funestus s.l.*, and *An. gambiae s.l.* are known to be primary vectors of *P. falciparum*, but have also been incriminated as vectors of *P. vivax* through the detection *P. vivax* circumsporozoite proteins in wild-caught specimens (Table 1.2). *Anopheles arabiensis* is often described as zoophilic, exophagic and exophilic, yet its behaviour appears to be quite variable, depending on location. For example, *An. arabiensis* found in West Africa are generally more anthropophilic and endophagic than those in the East. Such behavioural variability may enhance this species' ability to transmit *P. vivax* (or any human malaria) allowing it to adapt to avoid control methods such as IRS. Moreover, with peak biting times ranging from evening (1900) to early morning (0300), *An. arabiensis* may also avoid control via ITNs.

Anopheles arabiensis tends to be found in drier climates within Africa and larval habitats are typically small, temporary, clear, sunlit freshwater pools similar to those of *An. gambiae s.l.* However, *An. arabiensis* larvae have also been sampled from large or small man-made water bodies, including rice fields, as well as flowing or even brackish waters.

There is less variation observed in the bionomics of *An. funestus s.l.* relative to *An. arabiensis*. This species is known to be highly anthropophilic and endophilic and have a late biting time (after 2200), making IRS or ITNs highly effective interventions (although pyrethroid resistance has now been reported (Hargreaves et al., 2000; Coetzee and Fontenille, 2004)). The larval habitats of the Funestus Complex tend to be large, permanent (or semi-permanent) bodies of freshwater such as a pond, lake edge or rice field, where the larvae use emergent plants as protection against predation. There is some variation in the behaviour of members of the complex and further investigations using molecular identification methods are needed to determine the distribution of the different subtypes and the bionomics they exhibit.

Anopheles gambiae s.l. is perhaps the most well-known vector of human malaria and the most studied. It occupies a wide geographic range and is considered to be a highly efficient vector because of its highly anthropo-philic biting behaviour and relatively long adult life stage. Females generally feed late at night indoors and also rest indoors, again making IRS and ITNs successful intervention strategies. However, in studies comparing feeding and resting location preference, *An. gambiae s.s.* exhibited both indoor and outdoor feeding and resting habits (Sinka et al., 2010a). This is likely ascribed to different chromosomal and molecular forms now identified within the species (Bockarie et al., 1993). The larval habitats of *An. gambiae s.l.* were long thought to be restricted to clear sunlit, temporary pools such as puddles or hoof prints, however, larvae have been reported from turbid and even polluted water and from large semi-permanent water sources such as rice fields. The variation of larval habitats is again attributed to divergences of the chromosomal or molecular forms.

The vector species of *P. vivax* in Africa occupy wide geographic ranges across the region and exhibit variation in behaviours both among and within individual species or species complexes. This may present challenges for control, yet, the tendency for these species to bite and rest indoors at night makes control methods such as ITNs effective control strategies. Vivax malaria is not currently the main focus of malaria research in this region and incrimination studies on wild populations have yet to be performed on half

of the potential DVS in this region (Table 1.2). Further research identifying which anopheline species are the most efficient vectors of this parasite will be beneficial to the Africa+ region as goals of control and elimination of *P. falciparum* are realised and the focus moves to address *P. vivax*.

Africa+ summary. Estimates of the PAR of *P. vivax* in Africa, which is climatically well suited for malaria transmission, were very low, with the exception of countries around the Horn of Africa. This was because of the assumption that Duffy negative individuals, found in high frequencies on the continent (Howes et al., 2011), are refractory to *P. vivax* infection. This supposition was incorporated into the model, despite observations of *P. vivax* malaria infections in Duffy-negative individuals in Madagascar (Menard et al., 2010) and on the mainland of the continent (Ryan et al., 2006; Mendes et al., 2011; Wurtz et al., 2011). While this information contradicts our working assumption of complete protection, there is insufficient evidence to determine if these are more than just rare occurrences on the continent that would have a significant effect on the epidemiology of *P. vivax* in Africa.

Prevalence estimates for Africa are characterised by low predicted values and high levels of uncertainty (Fig. 1.4D). The PR data from Africa that served as the input data for the endemicity predictions were sparse, with the exception of a few regions (Fig. 1.3D1). This is largely because *P. vivax* is not the main priority for Africa. There were 753 million people at risk of stable *P. falciparum* in Africa in 2010 (Gething et al., 2011a), compared to the 38 million at stable risk *P. vivax*. However, 30% (228 million) of the 753 million were living in regions of low stable transmission (PfPR$_{2-10} \leq 5\%$); the prevalence of *P. falciparum* in these areas falls to a point where elimination is viable, the situation of *P. vivax* will increase relatively, a consequence of its tendency to be the last parasite standing during elimination efforts (Garnham, 1951; Yekutiel, 1960; Pampana, 1969; Wernsdorfer et al., 2009; Tatem et al., 2010). This reinforces the need for increased vector surveillance and incrimination of species specifically for *P. vivax*. The endemicity map (Fig. 1.3D2) presented indicates that while *P. vivax* is present at very low levels in Africa, it is circulating. Consideration for how those prevalence estimates may be affected by decreasing *P. falciparum* levels must be considered.

4.5. Areas Where Lack of Geographical Data is Acute

Asia. Although there was thorough coverage of annual clinical incidence data and a large number of prevalence data records, given the large area of *Pv*MECs in Central Asia (20.5 million km^2), there were still large regions with a dearth of data (Fig. 1.3A1). These regions are highlighted by the

uncertainty maps (Fig. 1.4A). India, the nation with the largest PAR of *P. vivax* globally, had disproportionately little prevalence data available. Given that parts of India are predicted to experience intense transmission, high-resolution mapping is needed to identify foci of transmission and this will only be achieved through improved surveillance coverage or the release of data that have not been previously shared. The uncertainty map also highlights lack of data in Myanmar. Regions of high uncertainty, which were also present in the population-weighted estimates, correspond with areas plotted to be highly endemic ($PvPR_{1-99} > 7\%$). Improved certainty in predictions in this country would be beneficial as neighbouring Thailand and China work towards malaria elimination. There would also be utility in the provision of contemporary data as progress towards elimination is made (e.g. in China) and transmission dynamics are therefore altered.

Asia-Pacific. Coverage of annual clinical incidence and prevalence survey data was relatively strong for this region (Fig. 1.3B1). However, the vast majority of the prevalence data originated from Indonesia. Sites on the island of New Guinea and parts of Borneo had very sparse prevalence data and were therefore predicted with greater uncertainty (Fig. 1.4B1 and B2). These regions have some of the most intense *P. vivax* transmission settings in the world. Improved surveillance would help localise hotspots and generate prime targets for control. The Philippines should also be noted as being a region with high uncertainty that was retained even after accounting for population density in the predictions. The smaller islands of this region would benefit from improved vector data collection since many had very little vector data available. This would improve the fidelity of the species distribution models in this region to better inform control decisions.

The Americas. Relative to other regions with stable *P. vivax* transmission, there were very little prevalence data available for this region (Fig. 1.3C1). Improved PR data from this part of the world, particularly those countries with intense transmission (Brazil, Honduras and Nicaragua), would benefit *P. vivax* mapping efforts. High-resolution mapping is needed to accurately map these highly focalized transmission settings, and this will require broad coverage survey data. There was good vector data coverage in this region, which is likely linked to the research and implementation of successful vector control efforts in the Americas. However, data collection on vector occurrence could be further improved. Some of the countries with the highest transmission (Honduras and Nicaragua) had the fewest occurrence records available.

Africa+. The *P. vivax* data available from Africa+ were also sparse, a reflection of the perception that the parasite is largely absent from the continent

(Fig. 1.3D1). In this region, the importance of *P. vivax* is overshadowed by *P. falciparum* and as such is not recorded in many countries. However, *P. vivax* infection has been observed in Duffy-positive and –negative individuals in the region, hence, it would be prudent for countries to monitor the prevalence of the parasite. While prevalence data were lacking from the region as a whole, the areas that would benefit most from improved surveillance are those with higher intensity transmission: Ethiopia, Madagascar and Somalia. This would reduce the uncertainty of the predictions and allow for better monitoring of control efforts. Lastly, the vector data available for the DVS in the region was relatively poor. Although the vector profile of Africa+ is straightforward, increased occurrence records may capture intricacies in distribution patterns and help distinguish vector and non-vector species of species complexes.

5. DISCUSSION

Plasmodium vivax malaria imposes serious public health burdens and is the most widespread of all the human malarias, particularly in women and children in poorly resourced communities (Poespoprodjo et al., 2008, 2009). Robust evidence demonstrates that *P. vivax*, despite long-held convention, is not a 'benign' infection (Baird, 2007; Price et al., 2007b). Moreover, studies show that 60-year-old drugs used to treat vivax malaria are failing throughout much of the *P. vivax*-endemic world (Baird, 2009; Price et al., 2009). The hypnozoitocidal component of that treatment, primaquine, is a deeply flawed therapy due to the threat it imposes to G6PD deficient patients (Baird, 2007). The reader is also referred to the chapter by Howes et al. that appears elsewhere in this thematic issue of *Advances in Parasitology* (Chapter 4, Volume 81). These issues are brought into focus as international targets, such as the Millennium Development Goals (http://www.mdgmonitor.org/), are developed to halt or mitigate malaria incidence and further goals are set for the elimination of the disease (WHO, 2007; Feachem and Sabot, 2008; The Global Health Group and the Malaria Atlas Project, 2011). Neglect of the impact and study of *P. vivax* is incompatible with these expressed goals.

The *P. vivax* PR estimates reviewed here are, across the American, African and Asian regions, uniformly low in comparison with PR estimates derived for *P. falciparum* (Gething et al., 2011a). The PR spectrum for *P. vivax* ranges from 0% to 7%, whereas for *P. falciparum*, it is 0 to 70%. This seems to imply *P. falciparum* transmission is an order-of-magnitude greater,

but this is potentially misleading. The absolute prevalence of *P. vivax* in heavily endemic zones may also reach or exceed 70%. Relatively low parasite densities in blood (arising from its strict preference for reticulocytes) may lead to high rates of false-negative diagnoses by microscopy or rapid diagnostic tests (RDTs) (Mueller et al., 2009a). Microscopic diagnoses very often underestimate the true prevalence of *P. vivax* in blood in both high- and low-transmission settings (Mueller et al., 2009b; da Silva et al., 2010; Harris et al., 2010; Katsuragawa et al., 2010; Steenkeste et al., 2010). Further details regarding the diagnosis of *P. vivax* may be found in a review elsewhere in this thematic volume of *Advances in Parasitology* (Chapter 4, Volume 80). Missed diagnosis is important in mixed species infections where *P. vivax* may be a minor contributor to parasitaemia and often overlooked (Mayxay et al., 2004). There is no proven evidence that this is due to cross-species immunity, rather that plasmodia species are mutually suppressive in mixed infections (Richie, 1988). While *P. falciparum* tends to dominate *P. vivax*, infection with *P. vivax* reduces the intensity of falciparum infections (Snounou and White, 2004). Mixed infections are complex and often under-diagnosed (Mayxay et al., 2004) and it is difficult to interpret the effect they may have on prevalence estimates. The reader is referred to a review of acquired immunity to *P. vivax* provided in this volume (Chapter 3, Volume 81).

The difference in PR spectrums between *P. vivax* and *P. falciparum* could also be a reflection of the age range used as the input data for the endemicity model. To model endemicity, *P. vivax* predictions were standardised across the 1–99 age range, rather than the 2–10 years of age range, which was used for *P. falciparum* (Gething et al., 2011a). Malaria transmission peaks in 2–10-year olds and, therefore, the use of the 1–99-year age range 'dilutes' the prevalence estimates. Regardless, it is evident that the association between the risk of disease and parasite prevalence is markedly different for *P. vivax* than *P. falciparum*, with significant risk of *P. vivax* disease at lower parasite densities.

The maps reviewed here represent progress towards an improved understanding of the epidemiology of this unique malaria parasite. Included in this work is the first ever *P. vivax*-specific global endemicity map and updated limits of transmission. These maps are intended to aid control strategy formulation and operational decision-making. Stratification by transmission intensity has been supported by mathematical modelling in the context of *P. falciparum* management (Smith et al., 2006, 2008; Okell et al., 2008; Smith and Hay, 2009; Chitnis et al., 2010a, 2010b; Griffin et al., 2010; Ross et al., 2011), but *P. vivax* is rarely differentiated by endemicity level.

Consensus has yet to be reached in defining suitable control-oriented strata for *P. vivax*. Without such stratified control, there has been little impetus to fill that knowledge gap and generate reliable stratified risk maps. These *P. vivax* mapping efforts may also be unified with those for *P. falciparum* (Hay et al., 2009; Gething et al., 2011a) to help rectify this and elucidate where control efforts of the two parasites can be amalgamated. An example of such is the potential use of artemisinin-combination therapy (ACT) as presumptive treatment for diagnosed malaria in co-endemic areas discussed in the review of the use of anti-malarial drugs to reduce *P. vivax* transmission that is provided elsewhere in this volume (Chapter 5).

Primaquine, the only drug currently licensed to treat the liver stage of the parasite is contraindicated in individuals with G6PD deficiency. The map of *P. vivax* endemicity is an important complement to the recently developed map of G6PD deficiency (Howes et al., 2012) and will help to identify areas with high prevalence of both *P. vivax* and G6PD deficiency. Overlaying these is essential for estimating the potential risk of adverse outcomes that could occur from treatment with primaquine in areas where G6PD deficiency testing cannot be guaranteed (Ruwende and Hill, 1998; Cappellini and Fiorelli, 2008). The reader is again referred to a review of G6PD deficiency that details the geographic distribution, genetic variants and the implication of primaquine therapy provided elsewhere in this thematic issue of *Advances in Parasitology* (Chapter 4, Volume 81).

Plasmodium vivax endemicity maps provide bench-marks for progress in control and elimination. This information is increasingly needed by international organizations and groups that are once again assessing the prospect of eradication of all species of human malaria (Lines et al., 2007; Feachem and Sabot, 2008; Greenwood, 2008; RBMP, 2008; Mendis et al., 2009; Malaria Eradication Research Agenda, 2011b). At present, these maps are of particular importance outside of Africa, where *P. vivax* is the primary threat. Thirty of the 95 *Pv*MECs are in Asia and their populations comprise 91% of the global PAR of *P. vivax*. Knowledge of the global distribution and impact of *P. vivax* is also important to estimate market size and investment priorities for those developing targets for drug (Malaria Eradication Research Agenda, 2011a) and vaccine (Brown et al., 2009; Malaria Eradication Research Agenda, 2011c) research and development. The maps also facilitate national priority setting and advocacy.

The maps of dominant vector species of human malaria presented here (Fig. 1.9) and information regarding the potential vector species of *P. vivax* (Table 1.2) highlight a further knowledge gap in our understanding of *P.*

vivax compared to *P. falciparum*. Classification of anopheline species as vectors of malaria has typically meant vectors of *P. falciparum* malaria. This is most evident in the Africa+ region, but conclusive information is also missing from the Asian and American regions, where *P. vivax* is the dominant parasite. In many countries, the status of vector species is determined by absence of evidence rather than decisive evidence of absence of the parasite. The research into transmission of *P. vivax* is lagging behind that of *P. falciparum*. Improved vector surveillance would benefit all regions, but not without incrimination studies that focus specifically on *P. vivax*.

Currently, the cartographic foundations for estimating the public health burden of *P. vivax* do not exist and this is perhaps the highest priority for moving forward. The link between *P. vivax* prevalence and clinical burden must be established for regions where the disease is monoendemic as well as where it is sympatric with *P. falciparum*. National estimates of *P. vivax* rely on routine case reporting sources that vary in their fidelity and are often crudely distinguished from *P. falciparum* (WHO, 2011). Cartographic estimates of *P. vivax* burden would provide valuable information regarding the impact of the disease independent of inherent biases that may accompany health system data (Gupta et al., 2009; Rowe et al., 2009; Hay et al., 2010a, 2010b; Malaria Eradication Research Agenda, 2011b; Mueller et al., 2011). There is also a need to define the burden of *P. vivax* in clinically vulnerable groups such as pregnant women (Nosten et al., 1999; Mueller et al., 2009a) and, most notably, children. To estimate the burden of *P. vivax*, it will first be necessary to gain a better understanding of the impact of relapsing infections on prevalence. The degree to which relapses contribute to clinical disease is known to vary geographically, but the cause and pattern of the variation is still poorly understood (Battle et al., 2011; Betuela et al., 2011; White, 2011) and calls for further investigation. The extent to which *P. falciparum* affects the burden of *P. vivax* remains unknown, and now emerges as an important question in elimination strategy (Maitland et al., 1996, 1997; Snounou and White, 2004; Genton et al., 2008).

This chapter described the global public health significance of *P. vivax* in light of new cartographic technology and evidence, along with the fundamentally important emerging understanding of the infection as threatens to life. The parasite occurs across a broader geographic range, in more diverse habitats, in more anopheline vector species, and threatens more people than *P. falciparum*. Vivax malaria is an overwhelmingly Asian and Asia–Pacific problem, home to 91% of the 2.49 billion PAR, dozens of mosquito vector species, and endemic habitats as distinct as the temperate Korean peninsula

and tropical New Guinea. This is the same region where treatments are failing due to drug resistance or reluctance to use threatening and impractical treatments like primaquine. Vivax malaria today threatens many people with very serious illness and is especially difficult to prevent and treat. The evidence presented in this chapter and others in this thematic issue disclaim the long-held presumption of inconsequence with infection by *P. vivax*.

6. METHODS

The full methods that would allow the reader to reproduce these maps are given in Gething et al. (2012) and Sinka et al. (2010b). Here, we bring together the full suite of methodologies and present a set of summaries that highlight the data used and the assumptions made to allow the value of the resulting estimates to be assessed.

6.1. Defining the Limits of *P. vivax* Transmission

To adequately assess the global burden of *P. vivax*, the limits of the infection and the global distribution of risk must first be identified. Knowledge of the spatial distribution, and the clinical incidence within those limits, provide a foundation on which control efforts and measures of progress can be based. MAP began these efforts through defining the spatial limits of infection and the PAR, informed by ecological variables and the distribution of Duffy negative individuals, and then applied those limits to mapping the transmission and varying levels of *P. vivax* endemicity globally.

6.1.1. International Limits of P. vivax

The global spatial limits of *P. vivax* malaria were first defined for 2009 (Guerra et al., 2010) and the methods and results have since been updated for 2010 (Gething et al., 2012). A list of 95 *P. vivax* malaria endemic countries (*Pv*MECs), illustrated in Fig. 1.10A1–D1, was identified using previous methods based on international health and travel guidelines (Centers for Disease Control and Prevention, 2009; Guerra et al., 2010; WHO, 2010b; Gething et al., 2011a). The *Pv*MECs were grouped into three regions: the Americas; Africa, Saudi Arabia and Yemen (Africa+); and Central and South East Asia (CSE Asia), which was further divided into Asia and Asia–Pacific in order to resolve PAR estimates (referred to here as Asia and Asia–Pacific) (Fig. 1.2). The borders of these countries, along with national survey information and relevant, published sources and personal communications, defined the first version of the *P. vivax* spatial limits map (Guerra et al., 2010).
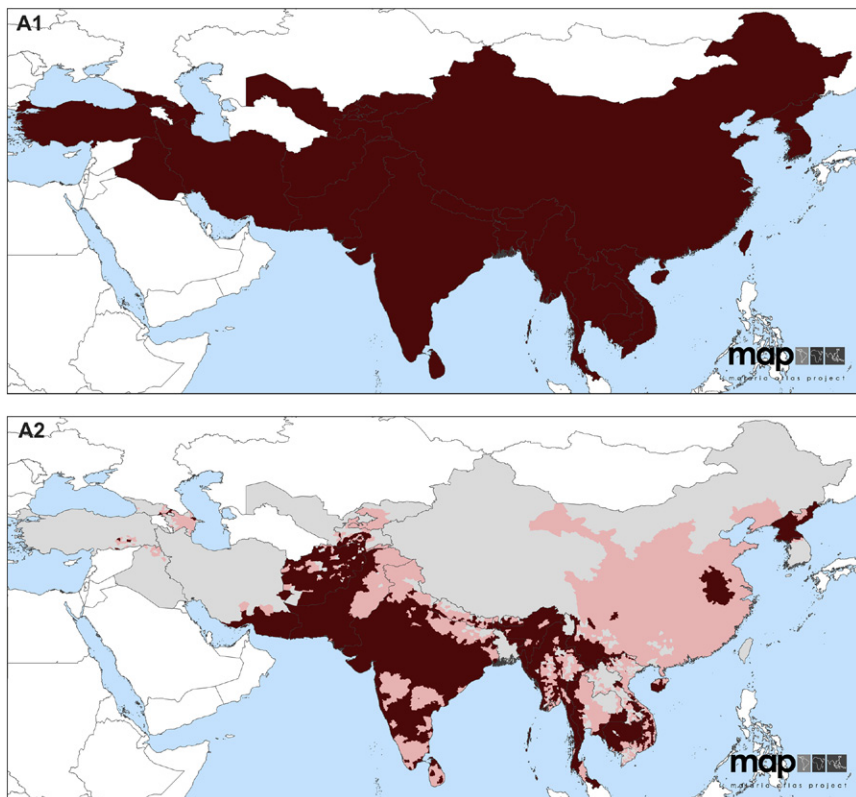
Figure 1.10 Map sequence illustrating the different exclusion layers applied by region. Maps are shown by region: Asia (A), Asia-Pacific (B), the Americas (C) and Africa+. Panel 1 = all regions of the regional *P. vivax* endemic countries; 2 = downgrading or exclusion of risk informed by annual parasite incidence data (*Pv*API); 3 = additional exclusion of risk informed by the biological temperature mask; 4 = additional downgrading or exclusion of risk informed by the aridity mask; 5 = additional downgrading or exclusion of risk informed by medical intelligence and international travel and health guidelines; 6 = the final limits definition after additionally downgrading risk in stable areas predicted to have very low prevalence by the model-based geostatistics (MBG) model. Stable transmission is shown in red, unstable transmission in pink, *P. vivax* malaria free areas in grey and countries non-endemic for *P. vivax* or outside of the region in white. For interpretation of the references to colour in this figure legend, the reader is referred to the online version of this book.

*Pv*API data, which report the number of confirmed *P. vivax* malaria cases per administrative unit per 1000 people per annum (p.a.) from *Pv*MECs, were used to further constrain the spatial limits of infection (Fig. 1.10A2– D2). *Pv*API data were obtained from a variety of sources which are provided in detail elsewhere (Gething et al., 2012). Data were unavailable for 41 of
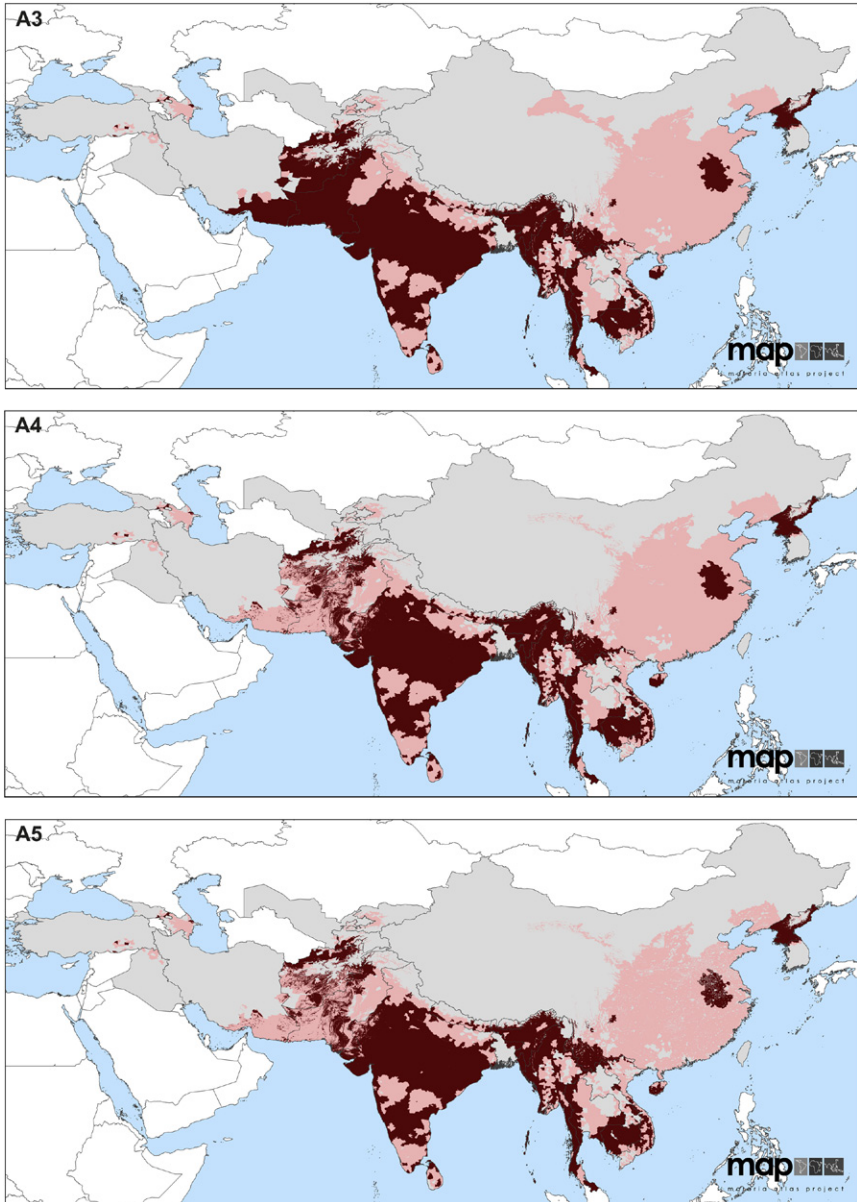
Figure 1.10, cont'd

the 95 *Pv*MECs, which were all within the Africa+ region, with the exception of Uzbekistan. Ideally, the *Pv*API data were available per administrative unit per year with each record containing information regarding the number of people in each administrative unit and the number of *P. falciparum*
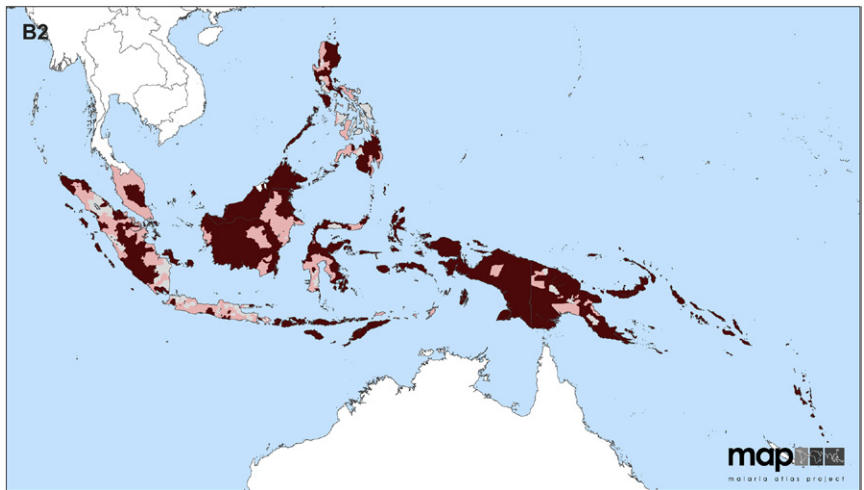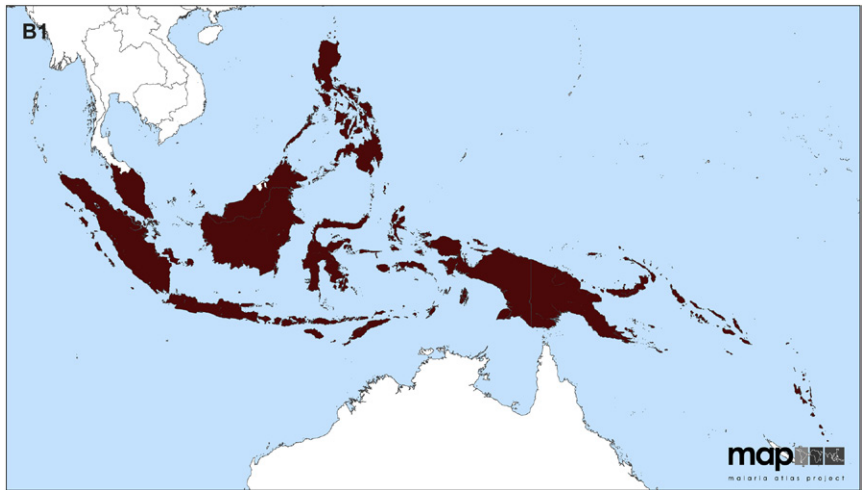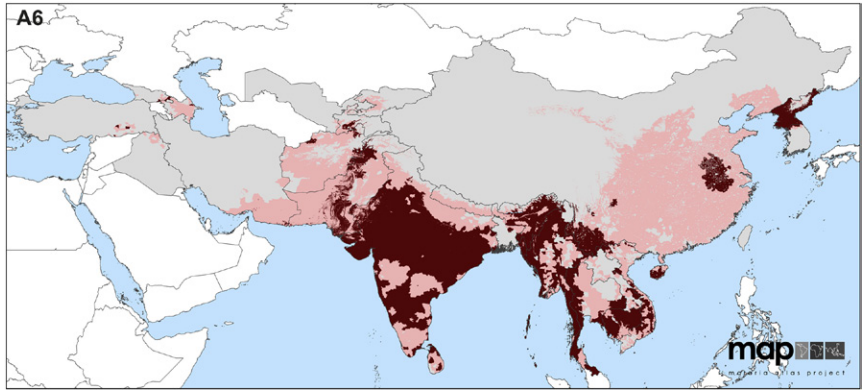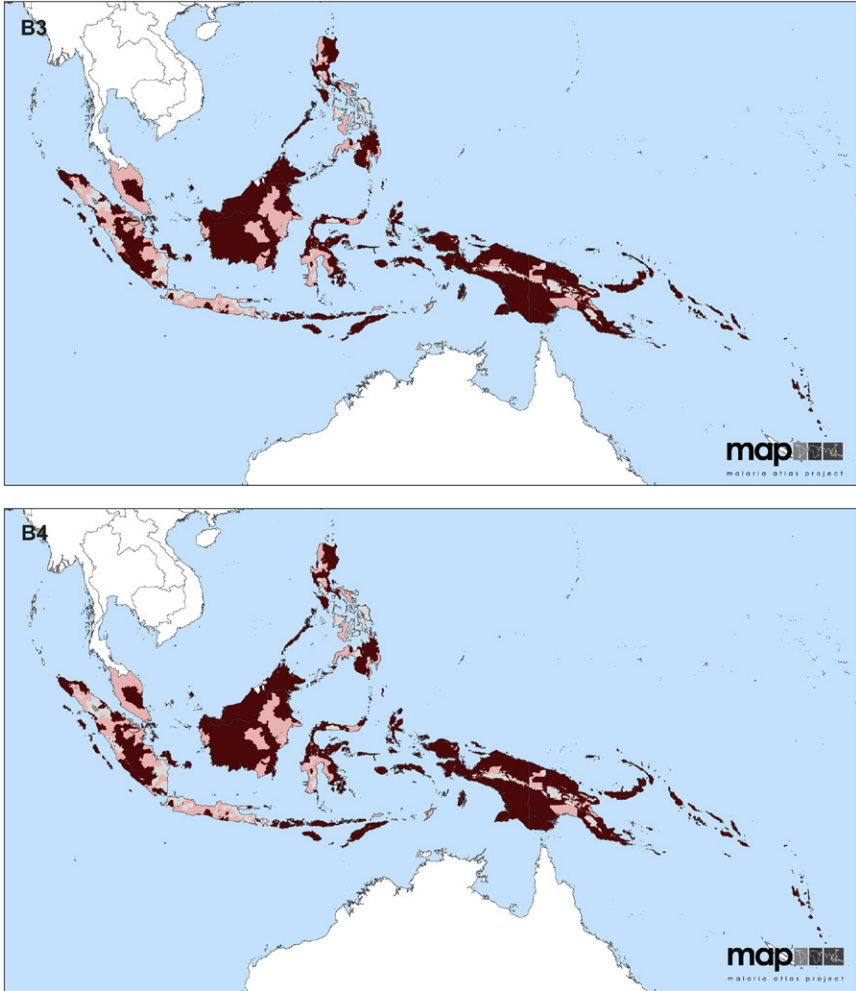
Figure 1.10, cont'd

Figure 1.10, cont'd

and *P. vivax* cases. When necessary, the missing data were extrapolated from
*Pv*API data estimates from preceding years or parasite species ratios con-
firmed by alternative sources. The aim was to obtain data for the four most
recent previous years (up to 2010) at the second administrative (ADMIN2)
level (or third, ADMIN3, if data were available). To map the *Pv*API data,
the information was reconciled to the digital administrative boundaries
available from the 2009 Global Administrative Unit Layers (GAUL) from
the Food and Agriculture Association of the United Nations (FAO) within
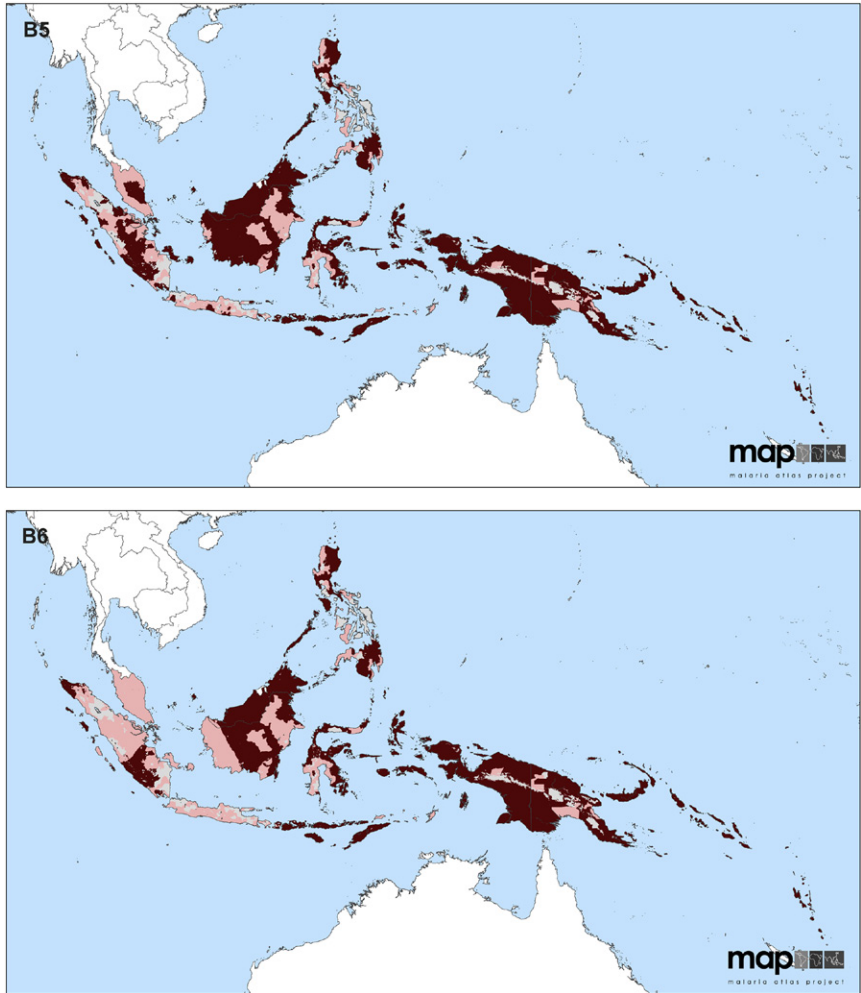the Food Security for Action Programme (FAO, 2008). *Pv*API data were

Figure 1.10, cont'd

arranged to classify areas at risk into three categories: malaria free, unstable
(<0.1 cases per 1000 p.a.) or stable (≥0.1 cases per 1000 p.a.) transmission.
These values were based on the Global Malaria Eradication Programme
classifications; API values of <0.1‰ were considered a reliable indication to
cease IRS and to shift to the consolidation phase of eradication (Pampana,
1969; Yekutiel, 1980; Guerra et al., 2008; Hay et al., 2008). This followed
a transition from a cut off of 0.5 cases per 1000 p.a., which was deemed
less reliable because malaria would at times return after the cessation for
spraying at an API of 0.5‰ (Guerra et al., 2008). This was likely because

Figure 1.10, cont'd

surveillance, whether passive or active, was not wholly reliable or reflective of true endemicity levels. The more conservative categorization that is also applied here, of unstable transmission equating to less than 0.1 cases per 1000 p.a. allowed for less confidence in the fidelity of the prevalence source information and accounted for inaccuracies in district or provincial level reporting (Snow et al., 2005; Erhart et al., 2007; Sharma, 2007).

Biological masks were applied to further constrain the risk in the *P. vivax* endemic regions. Environmental conditions can suppress malaria transmission by limiting various components of the transmission cycle. Temperature has been shown to affect vector survival, emergence and feeding rates (Ross, 1911; Detinova, 1962; Mahmood and Reisen, 1981; Ahumada et al., 2004). The most limiting effect of temperature on malaria transmission is the
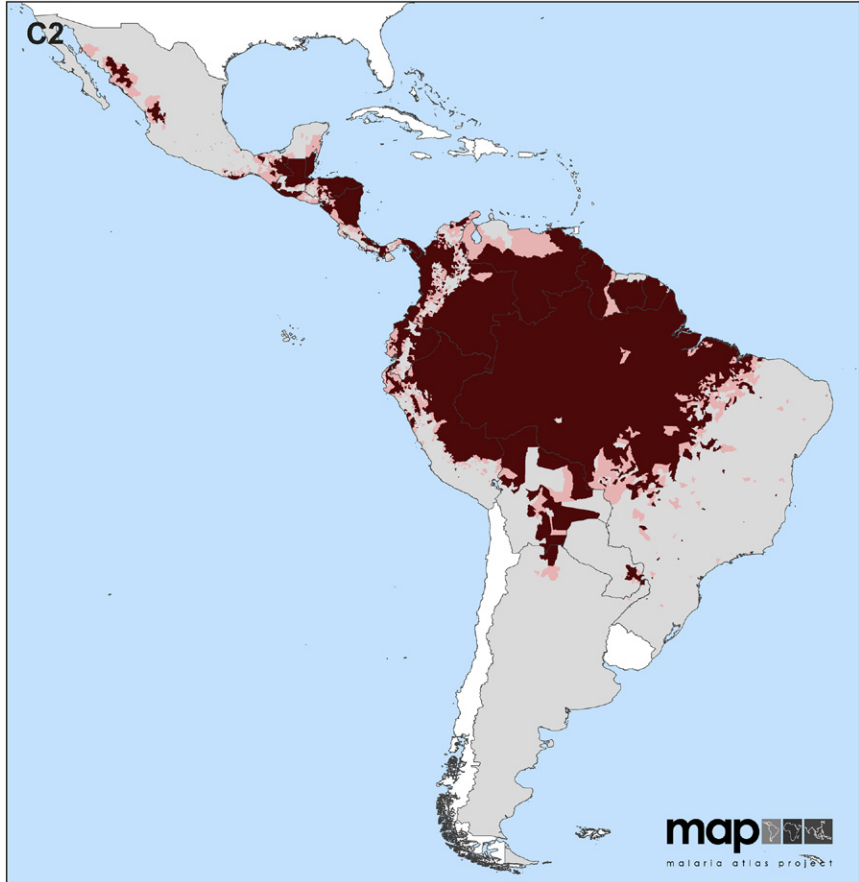
Figure 1.10, cont'd

interaction between vector lifespan and the length of the sporogonic cycle; as temperature varies throughout the year, as does the length of the extrinsic incubation period during which the parasite matures to the sporozoite stage within the gut of the mosquito (Nikolaev, 1935). For transmission to occur, the anopheline population must survive long enough for sporogony of the parasite to occur. A model that assesses the effects of temperature on *P. vivax* over time (Gething et al., 2011b) was used to generate a grid of temperature suitability proportional to vectorial capacity, a measure of transmission potential (Garrett-Jones, 1964; Smith and McKenzie, 2004). Daily vector survival was calculated as a function of local temperature and vector lifespan was assumed to be 1 month (Kiszewski et al., 2004), with exceptions being made for areas with longer living species (*Anopheles sergentii* and
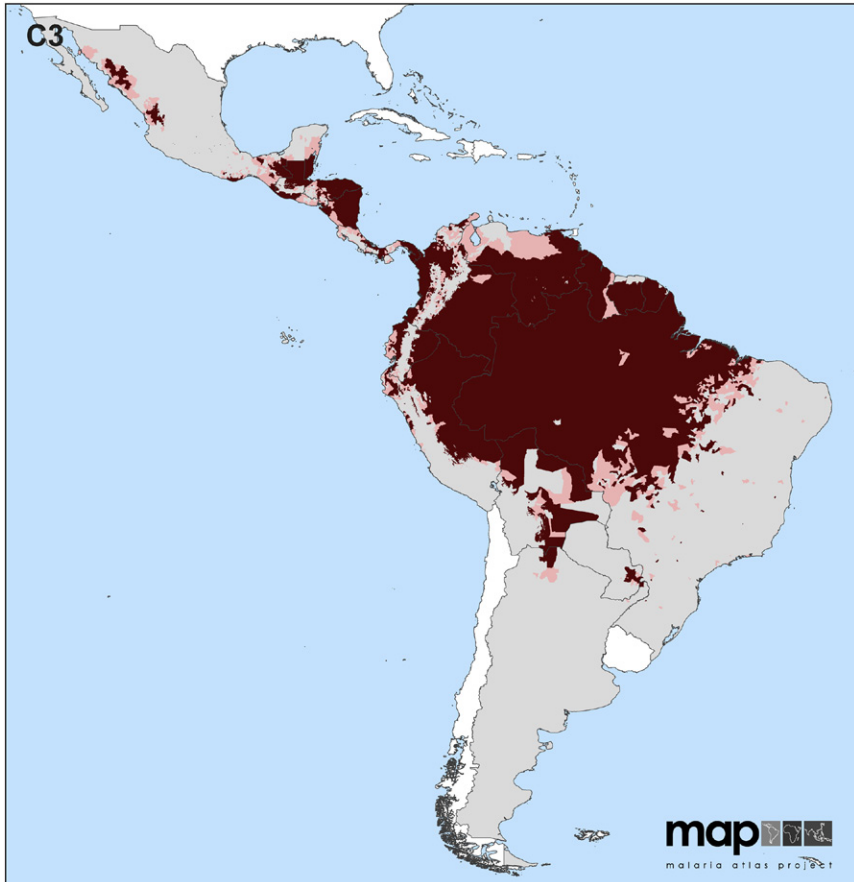
Figure 1.10, cont'd

An. superpictus) (Guerra et al., 2008; Sinka et al., 2010a). The interaction
between vector lifespan and the length of the sporogonic cycle was modelled
for each pixel of the temperature suitability grid (Fig. 1.5), so that pixels in
which there was no time during the year that sporogony could be completed
were classified as being at no risk for *P. vivax* transmission (Fig. 1.10A3–D3).

A second environmental driver of suitability for *P. vivax* transmission
is availability of sufficient moisture. A mask of aridity was used to exclude
areas where arid conditions would preclude anopheline survival at all life
stages (Shililu et al., 2004; Gray and Bradley, 2005). Arid areas were identified
using the global GlobCover Land Cover product (ESA/ESA GlobCover
Project, led by MEDIAS-France/POSTEL) (Bicheron et al., 2008). The
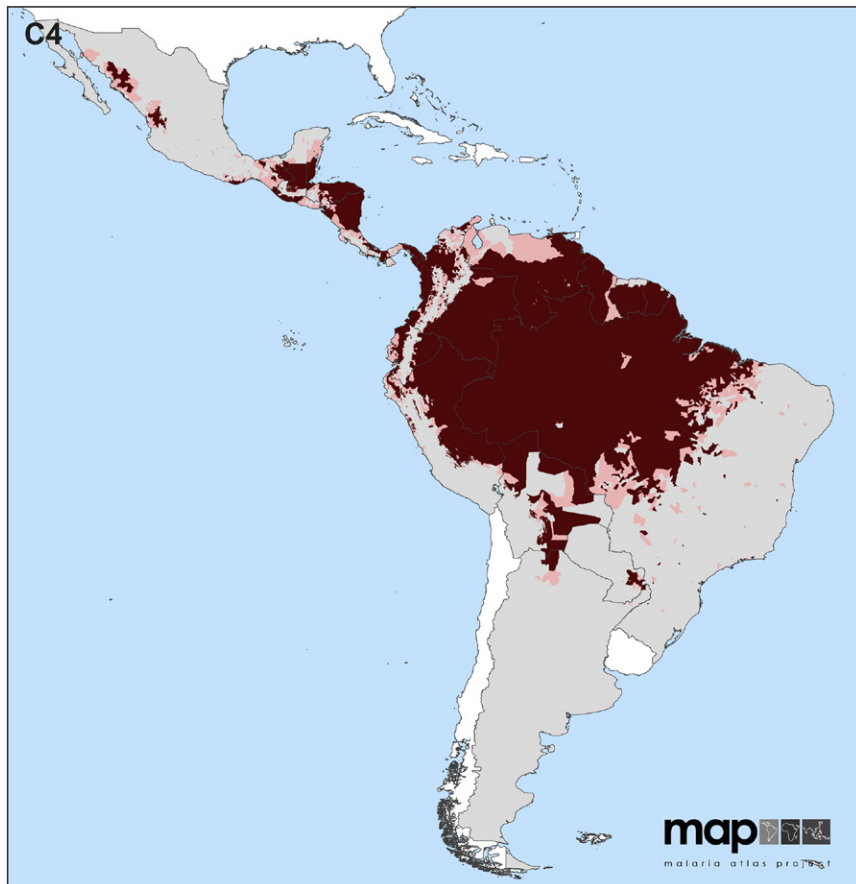aridity mask (Fig. 1.6) was treated differently from the temperature mask

Figure 1.10, cont'd

to accommodate for the possibility of human and vector species adapting to arid conditions so that risk classes were downgraded depending on the land cover. GlobCover bare areas classified as stable risk according to the *Pv*API were downgraded to unstable, and unstable risk was stepped down to malaria free (Fig. 1.10A4–D4).

Medical intelligence was also used to refine the limits of *P. vivax* risk (Fig. 1.10A5–D5). International travel guidelines (Centers for Disease Control and Prevention, 2009; WHO, 2010b) and data obtained through personal communications were applied to identify urban and sub-national malaria free-areas. Urban areas have less malaria transmission than rural areas because of the distinct ecological conditions that result from a man-made environment (Hay et al., 2005; Tatem et al., 2008). Different species
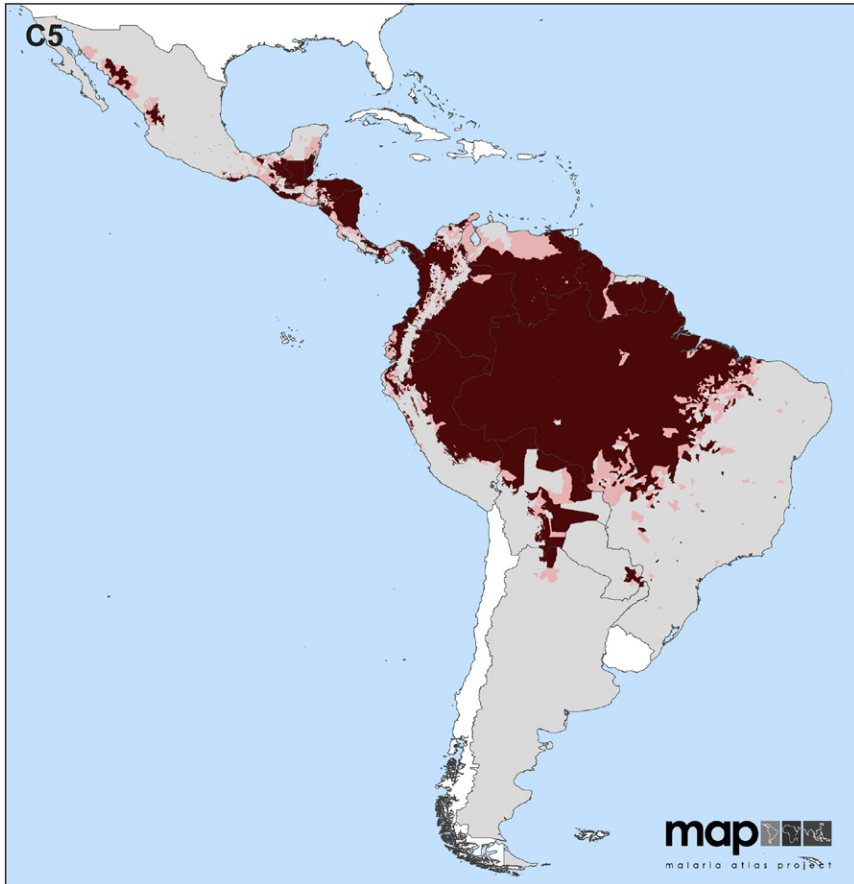
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of *Anopheles* mosquitoes respond at varying degrees, but urbanisation has been shown to reduce malaria transmission across Africa and in parts of the Americas (Hay et al., 2005; de Castro et al., 2006). In Asia, a principal vector, *An. stephensi*, has adapted to urban environments by breeding in artificial water collections (Sharma et al., 1993; Sinka et al., 2011) to the extent that stable transmission has been observed in the majority of cities (70 out of 86 cities examined) in India reporting annual parasite index data (Akhtar et al., 2009). *Anopheles culicifacies s.l.* has also been shown to transmit malaria in urban settings, but population densities and sporozoite rates indicate that this species is more affected by the environmental changes of urban areas (Nalin et al., 1985; Sharma et al., 1993; Sharma, 1995; Sinka et al., 2011). Therefore, it was assumed that urban transmission was maintained by only
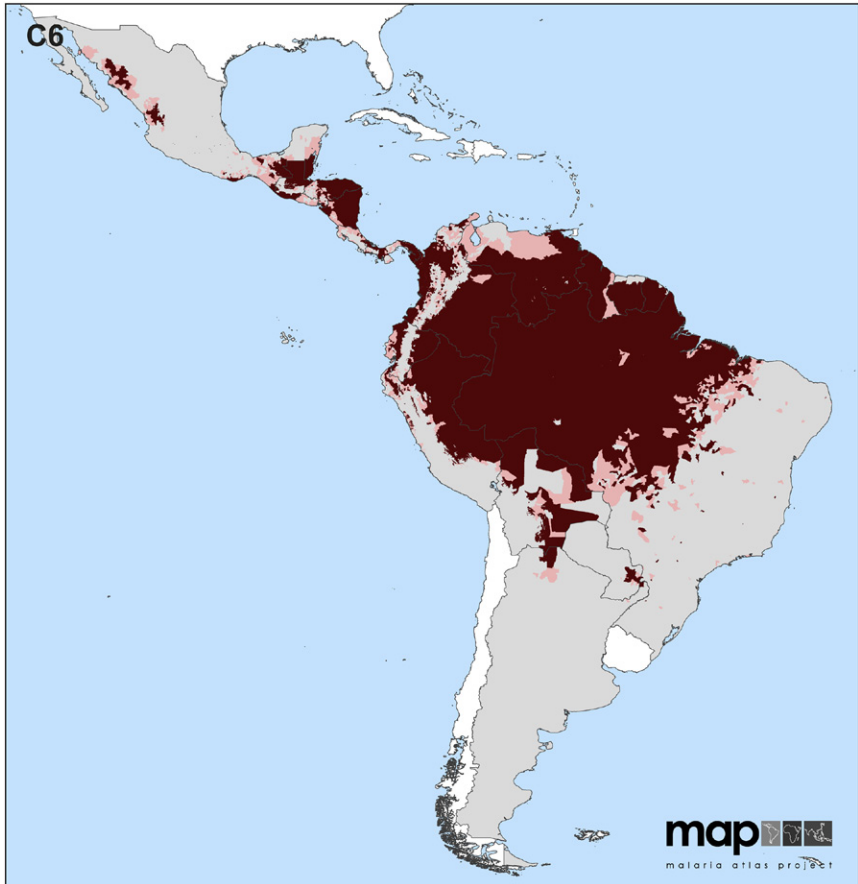
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An. stephensi. Cities specified as being malaria free by the international travel and health guidelines (Centers for Disease Control and Prevention, 2009; WHO, 2010b) or other sources were mapped using the GRUMP urban extent layer (Balk et al., 2006). Urban areas outside of the range of *An. stephensi* were classified as being at no risk of *P. vivax* transmission and areas within the vector species' range were down-graded by one risk level (stable to unstable; unstable to malaria free) accordingly. In addition to urban areas, some administrative areas, such as islands, were also declared malaria free by the international travel and health guidelines and a few specific personal communications. These areas were also classified as no risk if they were not already specified as such by the *Pv*API layer. The final limits for each region are shown in Fig. 1.10A6–D6.

Figure 1.10, cont'd

6.1.2. The Availability of PvAPI Data by Region

Plasmodium vivax API data were available from 53 countries at a variety of administrative levels from years ranging between 2002 and 2010.

Asia. Annual parasite index data were aggregated at a variety of administrative levels. Azerbaijan, Bhutan, Cambodia, Kyrgyzstan and Thailand provided data at the first administrative (ADMIN1) level. China reported data from areas known to have little to no transmission regions at ADMIN1, and at ADMIN3 in the remaining areas. Myanmar and Nepal reported all data from ADMIN3 units. The remaining countries (Afghanistan, Bangladesh, Georgia, India, Iran, Iraq, Lao PDR, Pakistan, Republic of Korea, Sri Lanka, Tajikistan, Turkey and Viet Nam) collected *Pv*API data from ADMIN2 units. *Pv*API data were available from 4443 risk units in Asia.
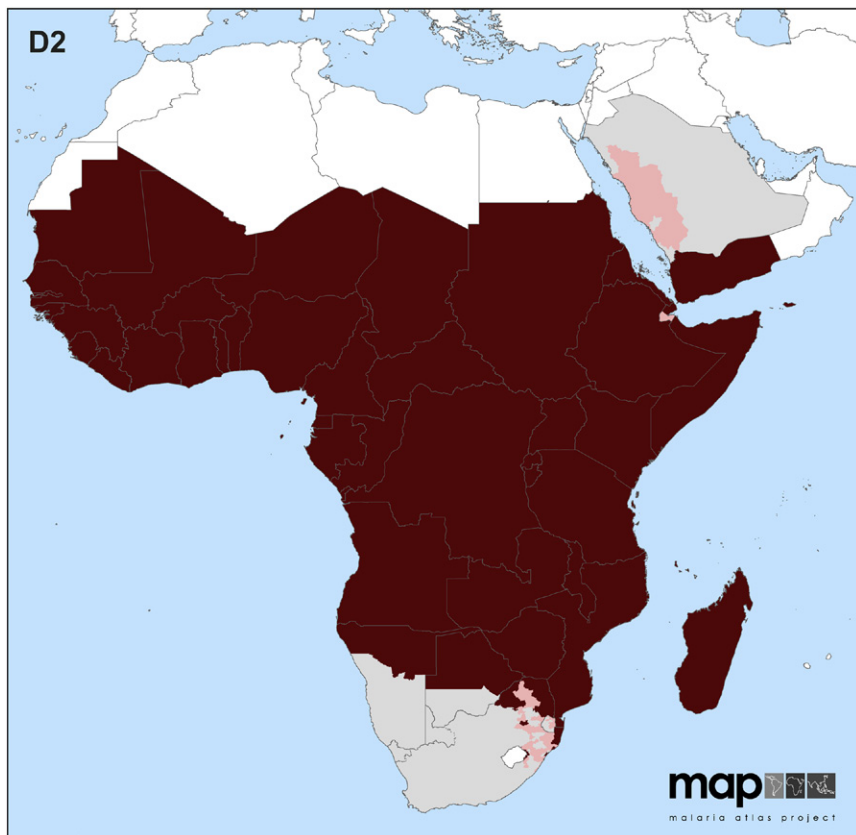
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Asia-Pacific. Annual parasite index data were provided for all of the *P. vivax* endemic countries in Asia–Pacific. Only Malaysia provided data up until 2010. Indonesia and Timor–Leste had data until 2008 available and 2007 was the last reporting year for the remaining countries. Malaysia, the Solomon Islands, Timor–Leste and Vanuatu provided data at the ADMIN1 level and Indonesia, Papua New Guinea and the Philippines reported data from ADMIN2 units. *Pv*API data were obtained from a total of 559 risk units in Asia–Pacific.

The Americas. *Pv*API data were available from all *Pv*MECs in the Americas. For the years reported, which varied by country, six countries (Belize, El Salvador, Guatemala, Guyana, Nicaragua and Suriname) reported data at the first administrative (ADMIN1) level and Venezuela reported data at the ADMIN1 and ADMIN2 level. Eleven countries (Argentina, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, French Guiana, Honduras, Mexico,
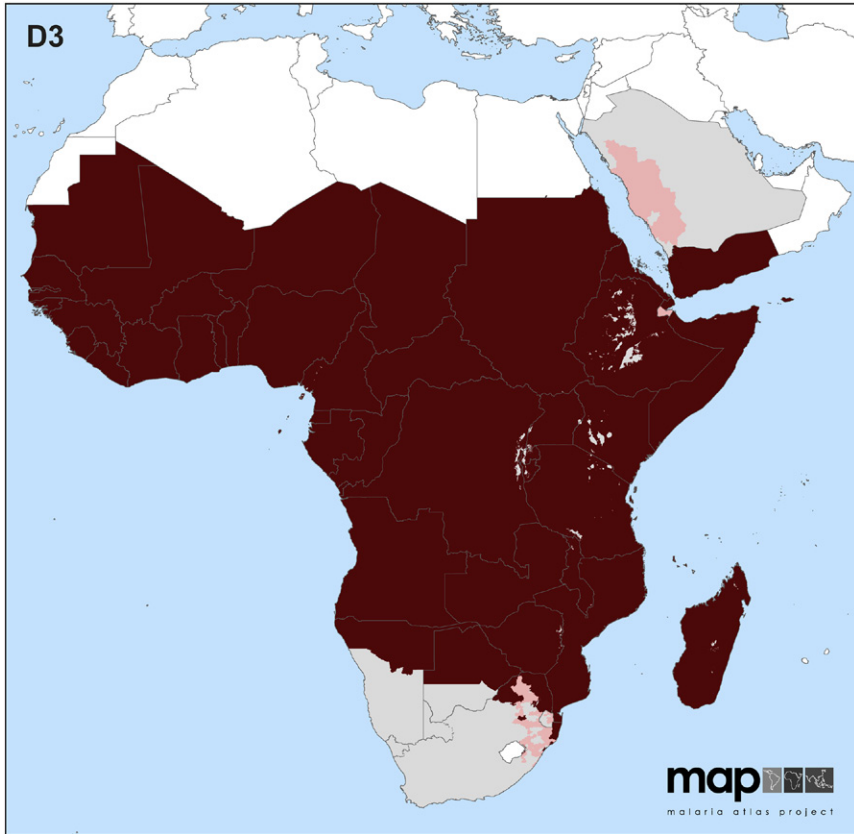
Figure 1.10, cont'd

Panama and Paraguay) reported ADMIN2 data and Peru reported data from ADMIN3 units. Data were available for a total of 12,514 administrative (or risk) units in the Americas.

Africa+. *Pv*API data were aggregated at a variety of levels by the six (out of 46) *Pv*MECs that reported data in the region. For the years of available data, Dijbouti, Saudi Arabia and Yemen reported ADMIN1 level data, Namibia reported from a mix of ADMIN1 and ADMIN2 units, and South Africa and Swaziland had data available at the ADMIN2 level. Data were provided for a total of 377 risk units for the Africa+ region.

6.1.3. The Global Distribution of the Duffy Blood Group

The distribution of Duffy-negative populations was used as another exclusion layer to constrain the limits of *P. vivax* transmission (Fig. 1.7). The reader
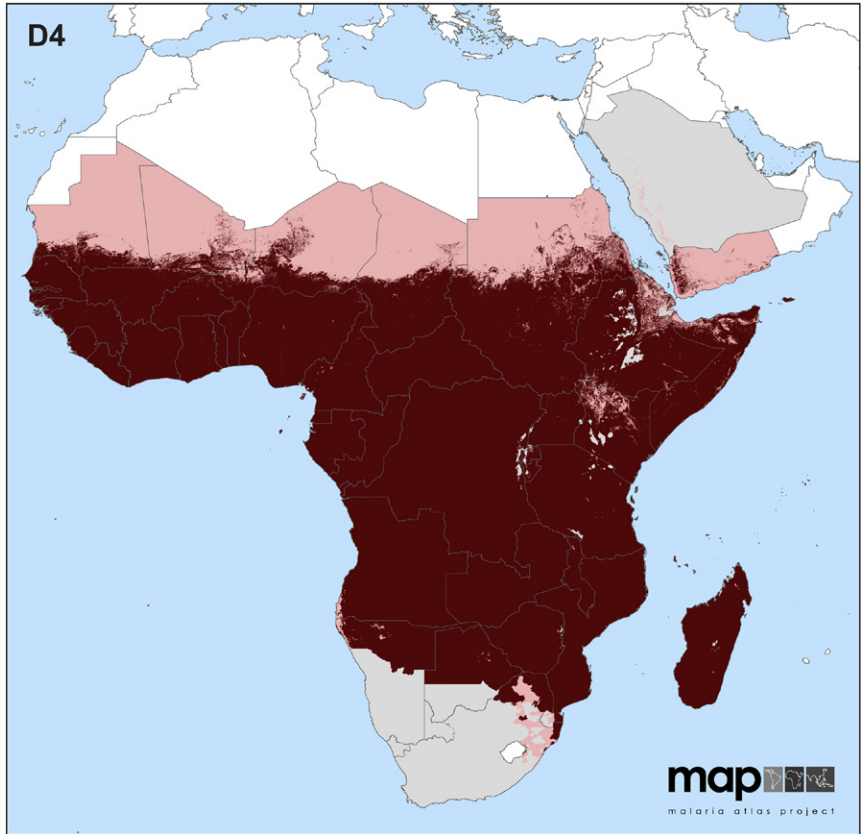
Figure 1.10, cont'd

is again referred to a detailed review of the effect of the lacking Duffy anti-gen on resistance to *P. vivax* provided in this thematic issue of *Advances in Parasitology* (Chapter 2, Volume 81). The Duffy antigen refers to a receptor expressed on the surface of red blood cells, which *P. vivax* has been shown to be dependent upon for erythrocytic invasion (Miller et al., 1976; Barnwell et al., 1989; Wertheimer and Barnwell, 1989). Duffy-negative individuals, who lack the antigen, are therefore largely refractory to *P. vivax* infection and high frequencies of the phenotype are presumed to suppress *P. vivax* ende-micity in areas that would otherwise be well suited for transmission. A con-tinuous map of the Duffy-negative phenotype, described in detail elsewhere (Howes et al., 2011) and briefly here, was used as the exclusion surface.

To model the global distribution of the Duffy-negative phenotype, a data-base of Duffy blood group surveys was assembled. Surveys of Duffy-variant
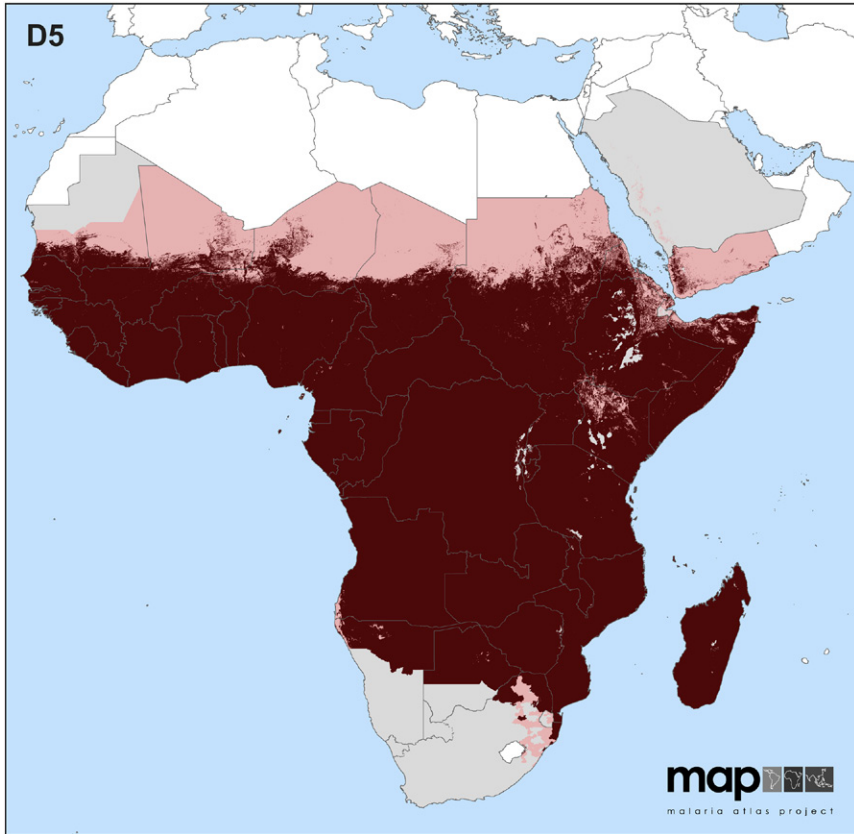
Figure 1.10, cont'd

frequencies were compiled from systematic searches of published literature, personal communications and sources obtained through previously published databases (Mourant et al., 1976; Cavalli–Sforza et al., 1994). Surveys dating back to 1950, when the blood group was first described (Cutbush and Mollison, 1950), were included. Results were refined so that only population-based surveys were used and potentially biased samples were removed. Survey data were geopositioned following guidelines described previously by MAP (Guerra et al., 2007).

In addition to the frequency of the blood group variants, the diagnostic method used in each survey was recorded to classify the type of information provided to ultimately inform the model. The Duffy antigen has two main variant forms, Fy^a and Fy^b. These differ by a single amino acid substitution (Gly42Asp), which is encoded in two alleles, $FY\star A$ and
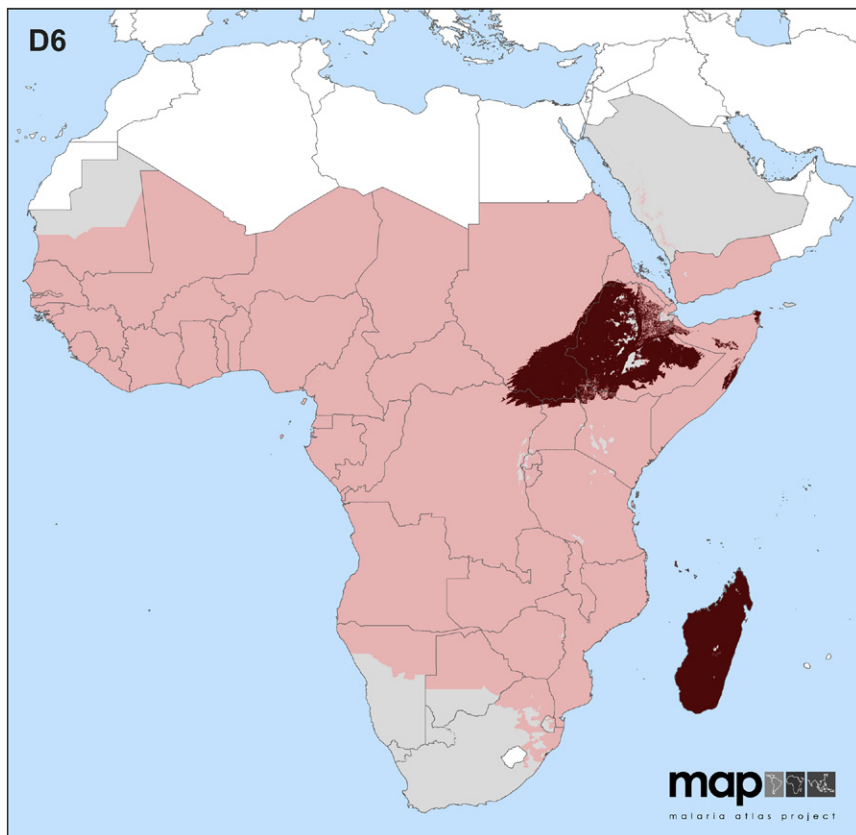
Figure 1.10, cont'd

FY★B, that vary based on a single base substitution (G125A) (Zimmer-man, 2004; Langhi and Bordin, 2006). A separate single base substitution in the gene's promoter region (T-33C) may block the expression of the gene and result in a null 'erythrocyte silent' (ES) phenotype. This mutation is most commonly associated with the *FY★B* (*FY★B^ES*) allele (the *FY★A^ES* allele is extremely rare) (Langhi and Bordin, 2006; Sellami et al., 2008). These four alleles (*FY★A*, *FY★B*, *FY★B^ES*, *FY★A^ES*) result in 10 possible genotypes and four possible phenotypes: Fy(a+b+), Fy(a+b−), Fy(a−b−) and Fy(a−b−) (Howes et al., 2011). Methods to diagnose Duffy types can focus on different aspects of the system: the individual polymorphic sites, the genotype, the presence or absence of the antigen, and which particular type of antigen is being expressed. The assembled data were therefore grouped into five types according to which diagnostic approach was used:

i) *Genotype*, where full genotypes were reported; ii) *Phenotype*, where full serological diagnoses (anti-Fy^a and anti-Fy^b sera) were used; iii) *Promoter*, if results only stated antigen expression or non-expression (no distinction between Fy^a and Fy^b); iv) *Phenotype-a*, if only Fy^a was tested for (no distinction between Fy^b and the negative phenotype); and v) *Phenotype-b*, if only Fy^b was tested for (no distinction between Fy^a and the negative phenotype).

This dataset formed the evidence-base for a geostatistical model used to predict a continuous map of the prevalence of the Duffy-negative phenotype [Fy(a−b−)], the phenotype encoded by the $FY\star B^{ES}/FY\star B^{ES}$ genotype. The $FY\star A^{ES}$ is highly infrequent and so was modelled as a small constant rather than a spatially variable allele. Although not all of the five data types directly informed the prevalence of Duffy negativity, the model was able to infer useful information directly from each (by ruling out certain genotypes), so all were included as model inputs. To allow this, the model structure was based on the frequencies of the two loci involved in the system: the promoter type (determining expression *versus* non-expression at the T–33C site) and the coding region (determining the G125A polymorphism). The Bayesian framework considered the two loci as spatially independent random fields, and used the survey data to map the frequency of the expression of each variant. Each of the data types informed different aspects of these loci: some informed both loci and others excluded possible variants. The model also incorporated a land cover variable to distinguish sub-Saharan African populations from others on the continent. This was to inform the model of the high probability of association between silencing mutation of the Fy^b variant and the $FY\star B^{ES}$ allele, which was observed in high frequencies across sub-Saharan Africa.

The Bayesian model-based geostatistical framework predicted Duffy group expression frequencies in all geographic locations across a 5 × 5 km grid to generate a continuous global surface of each variant. The Duffy negativity phenotype was expressed by the squared frequency of the $FY\star B^{ES}$ allele. The map reveals that the homozygous null phenotype is highly constrained to sub-Saharan African populations, with localized high-frequency areas in the Americas. Historical perceptions have supported the assumption that *P. vivax* is absent from much of the African continent (Rosenberg, 2007). However, evidence of autochthonous transmission within Africa indicated that areas of the continent should not be excluded a priori. This map, therefore, provided an evidence-based exclusion layer for Duffy-negative populations resistant to *P. vivax* infection in Africa.

6.2. Global Endemicity of *P. vivax*

6.2.1. P. vivax *Parasite Rate Data*

To map *P. vivax* malaria endemicity within the limits of stable transmission, in addition to the updated geographic boundaries and corresponding populations at risk of *P. vivax*, an updated georeferenced database of *P. vivax* parasite rate (*Pv*PR) survey data were compiled. PR was used here because it is the most ubiquitous of the malariometric measures of risk (Hay et al., 2009). *Pv*PR data represent the proportion of a randomly sampled population to have detectable *P. vivax* parasitaemia when screened via microscopy or RDTs and is the most consistently measured index of malaria endemicity. The final database consisted of unique surveys obtained from published and unpublished literature sources spanning the period 1985–2010. The database included information on the survey origin, how the location was determined (georeferencing method), time period, age group, sample size and diagnostic method used.

The *Pv*PR database was made up of 9970 spatiotemporally unique records from 432 different sources. Data were available from 53 countries, 12 of which were in the Americas, 19 in the Africa+ region, 15 in Asia and 7 in Asia–Pacific. There were 44 *Pv*MECs not represented in the database, most of which were in Africa, with the exception of Argentina, Azerbaijan, Belize, Bhutan, Korea DPR, El Salvador, Georgia, Guyana, Iran, Kyrgyzstan, Panama, Paraguay, Republic of Korea and Uzbekistan. Details of the PR data that were input into the model from each region are given below.

6.2.2. Modelling P. vivax *Endemicity*

To generate a continuous surface of *P. vivax* endemicity using PR data, a flexible modelling framework based on model-based geostatistics (MBG) (Diggle et al., 1998; Diggle and Ribeiro, 2007) was used. With areas of stable transmission converted into a 5 × 5 km grid, MBG models allow for endemicity values to be predicted at each pixel as a function of the geographically varying mean of survey values and a weighted average of neighbouring data values. MBG models are well suited for predicting endemicity values, in this case PRs, for a number of reasons. First, the mean PR values may be defined as a function of multiple environmental covariates that influence malaria transmission. Second, a covariance function may be employed to define the spatial heterogeneity of the PR data and, in turn, define the appropriate weight for each data point when generating a prediction. Third, uncertainty can be based on the nature and density of data surrounding a pixel. Fitting MBG models with Bayesian

inference and a Markov chain Monte Carlo (MCMC) algorithm produces uncertainty metrics around the final predictions as well as the model inputs in the form of predictive posterior distributions (Patil et al., 2011). Areas with the least uncertainty are those with a large number of recent surveys with relatively homogenous results, whereas greater uncertainty would be found in places with sparse or old surveys with ranges of different observed PRs.

To model a global endemicity surface of *P. vivax* malaria, an MBG framework that had been successfully employed for falciparum malaria (Hay et al., 2009; Gething et al., 2011a) was used following modifications made to accommodate biological features unique to *P. vivax*. The modelling methods incorporate surveys from a wide time period such that older surveys are given less weight than recent ones. The environmental covariates included were those that had an a priori expectation to affect malaria transmission intensity. These were urban areas defined by the GRUMP urban extent product (Balk et al., 2006; CIESIN/IFPRI/WB/CIAT, 2007), a long-term average vegetation index product used as a proxy for available moisture for vector reproduction and survival (Hay et al., 2006; Scharlemann et al., 2008), and the temperature suitability index derived from the model described above, which identifies areas suitable for transmission based on the requirements of vector survival and sporogony (Gething et al., 2011b).

PR data were standardised by age because of variation in infection rates observed in different age groups. It is often observed that malaria prevalence rises rapidly in infancy before reaching a plateau in early childhood and declining through adolescence and adulthood. This phenomenon was modelled using a previously described framework (Smith et al., 2007) to standardise for the prevalence variability among age groups. The model was informed with finely age-stratified *Pv*PR surveys to represent vivax-specific age profiles (Mueller et al., 2009b; Lin et al., 2010) and was used to convert all the observed survey prevalence values to standardised age–independent values for use in the MBG modelling. Predictions were made for all–age prevalence estimates for individuals aged one to 99 years ($PvPR_{1-99}$). Children aged <1 year were not included because of the potential confounding effect of maternal antibodies, but all other ages were included. This deviated from the method of using the 2- to 10-year cohort for falciparum malaria (Guerra et al., 2007; Gething et al., 2011a), because all age ranges are typically sampled for *P. vivax*, which is found at relatively lower prevalence rates.

To determine the endemicity of *P. vivax*, it was also important to incorporate Duffy negativity into the modelling framework because of the refractory nature of the phenotype to the parasite. The map of Duffy

negativity described above informed the model of the fraction of Duffy-negative individuals in the population at each pixel of the predicted surface. The parasite endemicity prediction could be made, therefore, from the vivax-susceptible or Duffy positive portion of the population. This meant that the proportion of *Pv*PR could not exceed the percentage of the population who were Duffy positive and that predictions in data-sparse portions of Africa could borrow strength from the Duffy negativity surface because estimates were limited to a more restricted range of potential outcomes.

The endemicity surface that results from the MBG modelling framework described is a 5 × 5 km grid of predictions for $PvPR_{1-99}$ within the limits of stable *P. vivax* transmission. For practical reasons, and because areas endemic for *P. vivax* have distinct ecological, entomological and epidemiological characteristics, the *P. vivax* endemic world was divided into four regions: the Americas, Africa+, Asia and Asia-Pacific. Separate models were fitted to each region so that a $PvPR_{1-99}$ estimate averaged across the 12 months of 2010 was found. The endemicity map was created by using the mean of each posterior distribution as a point estimate and uncertainty was shown as the ratio of the posterior distribution IQR to its mean. The IQR was found to express the precision with which the $PvPR_{1-99}$ values were predicted. Calculation of the ratio of the IQR of each posterior distribution to its mean generated an index that demonstrated how the model performance varied with data density in different locations. This index was also weighted by population density to generate a map to show where high levels of uncertainty may be operationally significant.

6.3. The Refined Population at Risk of *P. vivax*

The various data sources described above were combined to produce the final spatial limits map (Fig. 1.10A6–D6). After the implementation of MBG modelling, some of the regions that were estimated as being within the limits of stable transmission were downgraded to unstable transmission. If the model outputs of *Pv*PR were extremely low due to a large abundance of surveys reporting zero infections in that area or, in Africa, because of high Duffy negativity, a decision rule was applied such that pixels that were predicted with high certainty (probability >0.9) to be less than 1% *Pv*PR were reassigned as unstable.

The PAR of *P. vivax* malaria was estimated using the constrained limits of infection and population values for 2010 projected from the year 2000 GRUMP *beta* version population counts. The result was a 1 × 1 km spatial grid of population surface of the number of people living at stable or

unstable risk in each country as well as surface area of the regions at risk. The population surface, along with uncertainty maps, was also used to calculate a population-weighted index of uncertainty. The initial PAR based on the *Pv*MECs was 5.36 billion individuals in a land area of 69 million km². After applying the *Pv*API data (1.3 billion PAR excluded), temperature suitability (sporogony duration; 61 million PAR excluded), aridity (32 million PAR excluded), medical intelligence (713 million PAR excluded) and the Duffy negativity (768 million PAR excluded) layers, the remaining PAR was 2.49 billion in an area of 44 million km². This indicates that *P. vivax* was endemic across approximately a third of the world's surface. Half of that area was found in Africa (51%) and a quarter was in both America (22%) and Asia (27%). However, high population density in parts of Asia and the large proportion of the protective Duffy-negative phenotype found in African populations, meant that 82% of the 2.49 billion people at risk were in Asia with the remaining 17% being spread across Asia–Pacific (9%), the Americas (6%) and Africa (3%). Well over half of the PAR lived in areas of unstable transmission (62%; 1.52 billion) where transmission was very low and unlikely to exceed one case per 10,000 people per annum. A total of 965 million people were estimated to be living at risk of stable transmission. The endemicity maps (Fig. 1.3A2–D2) demonstrate that the transmission potential in and among stable transmission areas may vary greatly, even within relatively small geographic areas.

6.4. Mapping the Range of Dominant Vector Species

Vector distribution maps have long been used as a tool to aid malaria control globally. Examples of these maps date back to the 1950s and include vector species maps (May, 1951) and the ecological zones of malaria epidemiology determined by Macdonald based on climatology and known vector species ranges (Macdonald, 1957). More recent ecological (Mouchet et al., 2004) and global vector distribution (Kiszewski et al., 2004) maps have been widely adopted by the malaria research community. A recent series of publications by MAP has attempted to update malaria vector distribution maps with a comprehensive and extensive evidence base (Hay et al., 2010c; Sinka et al., 2010a, 2010b, 2011, 2012). There are 465 formally described species of *Anopheles* mosquitoes and more than 50 unnamed species and species complexes (Harbach, 2011). Approximately 70 species and species complexes have been incriminated to transmit malaria parasites (Service and Townson, 2002) and of those, 41 have been identified as DVS (Hay et al., 2010c). Determination of vector dominance is generally based

on factors that increase overall vectorial capacity (Takken and Lindsay, 2003), including abundance, propensity for feeding on humans and the mean adult longevity (to determine if the species lives long enough to transmit the parasite) (Hay et al., 2010c). In the process of determining vector dominance, it was noted which anophelines may have the potential to transmit *P. vivax*. A literature search of 'vivax' and the *Anopheles* species name was performed to identify evidence supporting wild transmission of the vivax parasite. The list of the *Anopheles* species, species complexes and groups as well as the evidence gathered regarding the potential for transmission of *P. vivax* are shown in Table 1.2.

To predict the geographic range of the 41 DVS of malaria, known occurrence points, expert opinion maps, ecological data and modelling techniques were applied. To begin, 15,837 occurrence records from 4800 sources were acquired from systematic searches of formal and informal literature sources and compiled into a comprehensive database (Hay et al., 2010c; Sinka et al., 2012). Expert opinion (EO) maps were then digitized from exhaustive searches of published maps, which are referenced in detail elsewhere (Sinka et al., 2010a, 2010b, 2011), and refined by consultation with a TAG. A suite of environmental and climatic variables known to shape vector distribution landscapes (such as elevation, land surface temperature and precipitation) were also included in the database (Sinka et al., 2010b). BRT modelling methodology (Elith et al., 2008) was applied to generate a predicted distribution map for each DVS. Distributions were generated for nine species/species complexes in the Americas; 13 for Africa, Europe and the Middle East; and 19 in Asia, 14 of which were in Asia (five were only in Asia), and 16 in Asia–Pacific (three were only in Asia–Pacific). Information was also gathered regarding the bionomics of the DVS, which greatly affects the potential impacts of common malaria interventions such as ITNs and IRS. Behaviours that were searched for and catalogued by species included larval site and habitat types, and adult resting and biting behaviours.

The predicted ranges of the DVS varied greatly across the regions, with relatively straightforward vector profiles in the Americas and Africa and very complex vector distributions across Asia. The distribution maps illustrate a probability of occurrence, but do not indicate the predicted prevalence. A positive (coloured) pixel does indicates that the probability of occurrence is >0.5 (>0.5 and ≤1.0) and that a negative pixel (not coloured/grey) represents a probability of occurrence <0.5 (0–0.5). The regional maps shown here are generated from an amalgamation of individual DVS distribution maps. The TAG identified the top three DVS per country (if the country

had more than three DVS) and ranked the DVS by their importance. Where there was great variation within countries (e.g. Indonesia), more detailed spatial information regarding the DVS was gathered. The rankings were then used to determine the order in which the species-specific distribution maps were layered to generate global-scale maps for the *Anopheles* vectors of greatest public health importance.

LIST OF ABBREVIATIONS

ACT Artemisinin-based combination therapy
ADMIN Administrative unit
Africa+ Africa, Yemen and Saudi Arabia
Asia Mainland Asia excluding the Malaysian Peninsula
Asia–Pacific The Malaysian Peninsula and the islands of Asia and the Pacific
CSE Asia Central and South East Asia
DVS Dominant vector species or species complexes
ELISA Enzyme-linked immunosorbent assay
G6PD Glucose-6-phosphate dehydrogenase
GRUMP Global Rural-Urban Mapping Project
IQR Inter-quartile range
Lao PDR Lao People's Democratic Republic
Korea DPR Democratic People's Republic of Korea
MAP Malaria Atlas Project
MBG Model-based geostatistics
MCMC Markov chain Monte Carlo
PAR Populations at risk
***Pv*API** *P. vivax* annual parasite incidence
***Pv*MEC** *P. vivax* malaria endemic country
***Pv*PR** *P. vivax* parasite rate
***Pv*PR$_{1-99}$** *P. vivax* parasite rate in 1–99-year olds
RDT Rapid diagnostic test
s.l. *sensu lato*
s.s. *sensu stricto*
TAG Technical advisory group

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