parameters of 0.25, 0.5 and 0.75 were used for each record, generating a total of 6 curve fits. We evaluated the first derivative of these fits at an interval of 3.125 days, the mean interval between satellite images. For each of the 6 derivatives, we defined two levels of sensitivity and identified peaks that exceeded these thresholds. For the 3 unfiltered Chl curves, sensitivities of 1 and 2 mg Chl m^{-3} per 3.125-day interval were used; for the GLM residual Chl curves, sensitivities of 0.1 and 0.2 were used for all but the least smooth (parameter = 0.75) record, where sensitivities were 0.15 and 0.25. The zero value following each threshold-exceeding peak in the derivative was defined as a bloom event. Each of these 12 models identified between 20 and 92 bloom events, with significant overlap resulting in identification of 121 total bloom events (Supplementary Fig. S1). Identified blooms that occurred within a sampling interval of 3.125 days centred on irrigation peaks were considered to occur concurrently with irrigation; lead and lag timing was calculated relative to this. All statistical analyses were performed in MATLAB.

Nitrogen deficit calculations

Nitrogen deficits were reported in the literature for the Eastern Tropical Pacific[4,5], the Benguela upwelling system[23] and the Arabian Sea[24]. For the GOC, Bay of Bengal and South China Sea, deficits were calculated using the ΔN formulation discussed previously[23] and based on data reported in the literature (GOC[7], Bay of Bengal[25] and South China Sea[26]).

Fertilizer data and projections

Data on use of N-based fertilizers was obtained from the United Nations Food and Agriculture Organization (FAO) Statistical Databases (http://apps.fao.org). World data includes all countries reporting to the FAO, and developing agricultural regions were defined as follows. Tropical Americas: Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Mexico, Nicaragua, Panama and Peru; Western Africa: Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Côte d'Ivoire, Democratic Republic of Congo, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Namibia, Niger, Nigeria, Republic of Congo, Senegal, Sierra Leone and Togo; South Asia: Bangladesh, Bhutan, India, Nepal, Pakistan and Sri Lanka; Southeast Asia: Brunei Darussalam, Cambodia, China, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam. Using a previously described approach[11], we found strong linear increases in fertilizer use over time in all regions, with r^2 values between 0.90 (Western Africa) and 0.97 (Southeast Asia). We projected these relationships forward to 2020 and 2050 to calculate fertilizer use.

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The global distribution of clinical episodes of *Plasmodium falciparum* malaria

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Interest in mapping the global distribution of malaria is motivated by a need to define populations at risk for appropriate resource allocation[1,2] and to provide a robust framework for evaluating its global economic impact[3,4]. Comparison of older[5–7] and more recent[1,4] malaria maps shows how the disease has been geographically restricted, but it remains entrenched in poor areas of the world with climates suitable for transmission. Here we provide an empirical approach to estimating the number of clinical events caused by *Plasmodium falciparum* worldwide, by using a combination of epidemiological, geographical and demographic data. We estimate that there were 515 (range 300–660) million episodes of clinical *P. falciparum* malaria in 2002. These global estimates are up to 50% higher than those reported by the World Health Organization (WHO) and 200% higher for areas outside Africa, reflecting the WHO's reliance upon passive national reporting for these countries. Without an informed understanding of the cartography of malaria risk, the global extent of clinical disease caused by *P. falciparum* will continue to be underestimated.

The Global Burden of Diseases programme of the WHO has attempted to enumerate the health consequences of malaria infection[8,9]. Because the African region has a notoriously weak system of reporting infectious diseases, epidemiological evidence from carefully conducted prospective, 'active' case-detection studies of malaria morbidity, disability and mortality in populations living

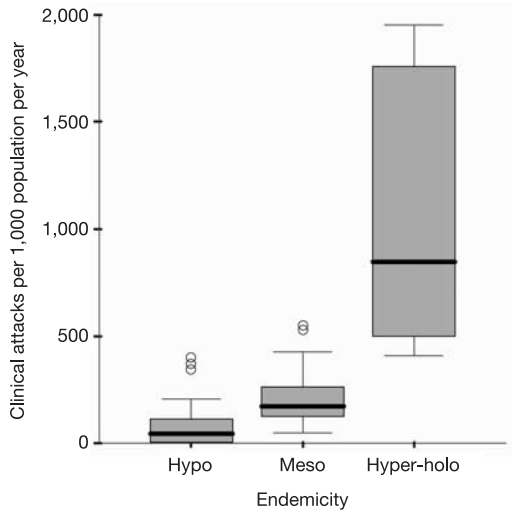

Figure 1 Annual clinical incidence of *P. falciparum* per 1,000 population according to hypoendemic ($n = 39$), mesoendemic ($n = 25$) and combined hyperendemic and holoendemic ($n = 8$) conditions. The box indicates the inter-quartile range (25% and 75%) and the thick line within the box represents the median. The whiskers represent the 2.5% and 97.5% centiles and outliers are plotted as circles outside this range. Three studies were excluded because they were undertaken in areas of a recorded zero *P. falciparum* prevalence, and each reported no clinical attacks due to *P. falciparum.*

under different transmission intensity risks have been compiled to estimate the disease burden[10]. A different approach was adopted for WHO regions outside Africa, where the burden was computed from 'passive' national disease and mortality notifications to WHO regional offices without precisely defining the populations exposed to varied malaria infection risks[9,11,12]. This use of national disease registration systems to provide accurate reflections of disease rests on three assumptions: that there is complete temporal coverage (every month is reported by a facility), that there is complete spatial coverage (every health facility reports nationwide), and that all disease events present to, and are reported by, health facilities. In reality, passive detection of disease events in most resource-poor countries is incomplete, even outside Africa.

Here we provide a standard global approach to deriving clinical malaria burden by using evidence of the epidemiological risks of disease outcome from active case-detection studies in combination with estimates of populations at risk of various *P. falciparum* transmission conditions. A comprehensive outline of these procedures is given in Methods. A conservative approach is defined to further account for the confounding of malaria diagnosis efficiency by endemicity (see Supplementary Information A for more detail and original data) and the modifying influence on endemicity of current levels of control and urbanization (see Supplementary Information B).

Our global model suggests that, in 2002, 2.2 billion people were exposed to the threat of *P. falciparum* malaria, resulting in a conservative estimate of 515 (range 300–660) million clinical attacks attributable to this parasite during that year (Fig. 1 and Table 1). At a regional level, most clinical events attributable to *P. falciparum* were concentrated in the African region (70%), but the highly populated South East Asia region contributed 25% of the world's clinical attacks in 2002 (Fig. 2 and Table 2). The WHO suggests that there were 273 million clinical attacks of malaria worldwide in 1998 and that 90% of the global disease incidence is borne by Africa[9]. Other WHO estimates report that in 1990 the global incidence of malaria was 213 million cases[13]. Neither of these sources provides sufficient detail on how the estimates were derived. Our models, by contrast, are both data-driven and reproducible. They also indicate that the number of clinical attacks due to *P. falciparum* might be 50% higher than WHO estimates, and highlight the fact that almost one-third of the global incidence occurs outside Africa.

We have not examined mortality attributed directly to *P. falciparum*, because of the paucity of prospective epidemiological descriptions of cause-specific mortality outside Africa[14]. The risk of death after a clinical attack of *P. falciparum* seems much higher in Africa than in South East Asia and the western Pacific. The incidence of severe, life-threatening complications of

Table 1 **Populations (millions) at risk in 2002**

Region	Population in *P. falciparum* endemicity classes				
	Unclassified	Hypoendemic	Mesoendemic	Hyperendemic and holoendemic	Total population at risk
Africa	13.6	39.3	67.4	414.3	521.0
Americas	3.5	43.9	10.5	0	54.5
South East Asia	47.8	827.6	486.0	0.3	1,313.9
Western Pacific	22.4	77.6	63.4	1.0	142.0
Eastern Mediterranean	32.3	143.0	33.4	0	176.4
Europe	1.1	0.3	3.2	0	3.5
Total world	120.7	1,131.7	663.9	415.6	2,211.3

Populations were determined according to classifications of malaria risk adjusted for urbanization by WHO region (see Supplementary Information B).

Table 2 **Estimated data for *P. falciparum* clinical malaria cases in 2002 (millions)**

Parameter	Hypoendemic	Mesoendemic	Hyperendemic and holoendemic	Total *P. falciparum* cases
Attack rate (per 1,000 population per year)	43 (6–117)	171 (125–261)	849 [500]	–
Cases per WHO region (millions)				
Africa	1.69 (0.24–4.60)	11.52 (8.42–17.58)	351.77 (207.17–351.77)	364.98 (215.82–373.95)
Americas	1.89 (0.26–5.14)	1.80 (1.32–2.75)	0	3.69 (1.58–7.89)
South East Asia	35.59 (4.97–96.83)	83.11 (60.76–126.86)	0.24 (0.14–0.24)	118.94 (65.86–223.93)
Western Pacific	3.34 (0.46–9.08)	10.84 (7.93–16.55)	0.85 (0.50–0.85)	15.03 (8.89–26.48)
Eastern Mediterranean	6.15 (0.86–16.73)	5.71 (4.17–8.71)	0	11.86 (5.03–25.44)
Europe	0.01 (0.00–0.03)	0.54 (0.40–0.83)	0	0.55 (0.40–0.86)
Total world	48.67 (6.79–132.41)	113.52 (82.99–173.28)	352.86 (207.81–352.87)	515.05 (297.59–658.55)

Results are medians and IQR (in parentheses) by WHO region and endemicity class, based on urban-adjusted denominators, derived from Table 1; the lower quartile (in square brackets) is presented instead of the IQR for populations living under conditions of hyperendemic and holoendemic transmission (see Methods).

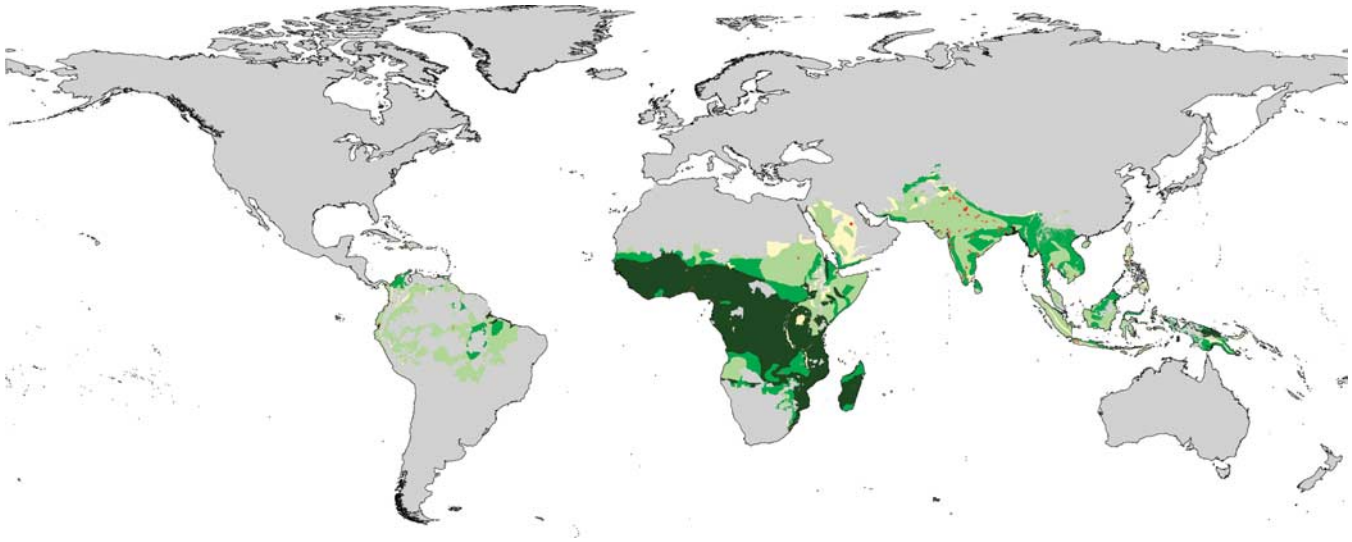

Figure 2 *P. falciparum* endemicity distribution within the global limits of risk. Endemicity classes: light green, hypoendemic (areas in which childhood infection prevalence is less than 10%); medium green, mesoendemic (areas with infection prevalence between 11% and 50%); dark green, hyperendemic and holoendemic (areas with an infection prevalence of 50% or more)[13]. Unclassified areas (yellow) represent only 6% of the global population at risk and are due to discrepancies between the 2002 delineation of risk and the endemicity risk limits developed in refs 6 and 7. Grey areas are a combined mask of areas outside of the transmission limits and areas of population density less than 1 person km^{-2} (ref. 16).

P. falciparum malaria in Africa[15] is at least tenfold that in similar malaria endemic areas in India[16] and Vanuatu[17]. Reasons for this are unclear but might include better access to prompt treatment[18] and some cross-*Plasmodium* species protection against severe disease outcomes[19].

We had estimated previously from epidemiological data that there were 221 million *P. falciparum* attacks in Africa in 1995 (ref. 10). Our 2002 estimate for Africa of 365 million clinical cases derives from a more specific, urban-adjusted endemicity map than that developed specifically for Africa in 1995, which was not structured according to levels of parasite prevalence. It was estimated[12] from national statistics that there were 51.2 million *P. falciparum* cases outside Africa in 1995; our estimate of 150 million cases is considerably higher. There are several possible explanations for this disparity, including our assigning populations at risk of different transmission conditions on the basis of an endemicity map constructed in 1968. We have used this map in its original form because there is no modern equivalent but have taken a very conservative approach to reclassifying areas at risk in 2002 by stepping down endemicity risks in all areas outside Africa and allowing for the rapid increases in urbanization since 1968. Furthermore, the clinical data on active detection of cases were derived from a wide range of malaria endemicities (see Supplementary Information A) to create plausible endemicity-specific median estimates of disease. It seems unlikely that we have overestimated the clinical risks when reapplied to the global distributions of the three broad endemicity classes.

The most obvious explanation is the dependence on national statistics derived from passive detection of cases for the WHO's present global disease estimates outside Africa. In our analysis we were able to compare WHO reports of clinical incidence from 12 administrative units with survey reports of data on active case detection in the same areas. These limited comparisons demonstrated the scale of under-reporting by passive detection, varying from a threefold difference in Brazil to a 1,000-fold difference in Pakistan.

The global Roll Back Malaria (RBM) initiative aims at halving the burden of malaria within the next six years[9]. The Millennium Development Goal's target is to halt the rising incidence of malaria by 2015 (ref. 20). To achieve this, international priorities and resources must be targeted using different information sources, including national economic capacities, evidence-based cost-effective strategies and disease burdens. Inadequate descriptions of the global distribution of disease risk make it impossible to determine priorities and advise funding agencies appropriately. Redressing these deficiencies with robust data must be a priority if international agencies are to understand the size of the challenge set by their targets over the next ten years. □

Methods

To identify reports of *P. falciparum* morbidity risks defined through epidemiological studies, an electronic data search was undertaken through PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) using the keyword 'malaria' in conjunction with each country name in all WHO regions. Abstracts were reviewed to identify reports of malaria morbidity incidence, and full papers were obtained for all original reports, or cross-referenced sources, that met the following selection criteria: first, that the report covered the period after 1985; second, that the study involved active detection of cases with the use of clinical or epidemiological morbidity definitions; third, that it was possible to compute the numbers of cases confirmed microscopically and the numbers of person-years of observation; and last, that data were reported for all age groups to capture the cumulative incidence from birth until adulthood in communities with different age-specific incidence patterns. Using these criteria for inclusion we identified 83 independent annual incidence estimates of *P. falciparum* clinical attacks from 22 countries in five WHO regions (see Supplementary Information A). No data were identified from Tajikistan, the only country in which *P. falciparum* malaria transmission occurs in the European region.

Infection prevalence has been used since the 1950s to describe malaria endemicity categorically[21]. We therefore identified coincidental cross-sectional measures of *P. falciparum* infection prevalence within the original morbidity reports, or associated publications, and matched these to 75 communities where rates of clinical attack had been established (see Supplementary Information A). *P. falciparum* annual rates of clinical attack were summarized as medians and interquartile ranges (IQR) to allow for the ranges and uncertainty of survey estimates within three infection prevalence classes: hypoendemic (parasite prevalence less than 10%), mesoendemic (parasite prevalence between 11% and 50%) and combined hyperendemic and holoendemic (parasite prevalence 50% or more) (Fig. 1). Epidemiological case definitions in areas of hyperendemicity to holoendemicity pose difficulties where fever and infection are common but are not necessarily related causally. We have adopted a working clinical definition in all malaria endemicities of fever in the presence of patent peripheral infection, accepting that this will overestimate the incidence of clinical disease in areas of hyperendemic to holoendemic transmission. To accommodate overestimation in areas of high transmission we have used the lower quartile and median as a more conservative and biologically plausible range of clinical risk.

To define the congruence of human population distribution and *P. falciparum* transmission we used spatially linked databases of human population, limits of malaria risk and malaria endemicity within a Geographic Information System (GIS) as outlined in detail in Supplementary Information B. In brief, we first defined the spatial extent of *P. falciparum* risk by using the mapped global limits of malaria risk provided by the WHO[22] and modified with contemporary descriptions of spatial risk used to inform antimalarial chemoprophylaxis regimes in travellers[22,23], to exclude the following: countries with only *P. vivax* transmission, areas above anopheline vector-specific altitude limits, and administrative areas defined as risk-free. These boundaries formed the limits of *P. falciparum* risk and were overlaid on the only available global map of malaria endemicity developed in 1968 (refs 6, 7). This map was part of a major synthesis of historical records, documents and maps of malaria endemicity (using the hypoendemic to holoendemic classifications) interpolated globally for malaria at the peak of its assumed historical distribution. We have assumed that this endemicity map is consistent with contemporary malaria risks in Africa, but development and intervention will have substantially reduced malaria risk elsewhere[11]. Outside the African region we consider the historical (1968) hyperendemic to holoendemic areas as contemporary (2002) mesoendemic conditions, historically mesoendemic areas as hypoendemic, and hypoendemic risk areas at their historical descriptions within the revised 2002 spatial limits of risk.

Data from Gridded Population of the World (GPW3) version 3.0 beta (http://sedac.ciesin.colombia.edu/gpw) were projected to 2002 by using national inter-censal growth rates from the UN Population Prospects database (http://esa.un.org/unpp). Population totals were extracted by country for those residing in hypoendemic, mesoendemic and hyperendemic-to-holoendemic settings (Table 1, Fig. 2). These population totals were further adjusted for the suppressive effects of urbanization on malaria transmission[24] by identifying all urban areas with populations of more than 1 million. Urban population totals within these pixels were reclassified to the risk class below their original classification; thus, those located in hypoendemic areas were regarded as being at no infection risk. Populations in 2002 residing in the different urban-adjusted, *P. falciparum* endemicity risk zones are shown in Table 1. The endemicity-specific morbid risks were then applied to populations within their respective endemicity classes to estimate numbers of clinical events in 2002 (Table 2).

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Mediation of pathogen resistance by exudation of antimicrobials from roots

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Most plant species are resistant to most potential pathogens. It is not known why most plant–microbe interactions do not lead to disease, although recent work indicates that this basic disease resistance is multi-factorial[1,2]. Here we show that the exudation of root-derived antimicrobial metabolites by *Arabidopsis thaliana* confers tissue-specific resistance to a wide range of bacterial pathogens. However, a *Pseudomonas syringae* strain that is both at least partly resistant to these compounds and capable of blocking their synthesis/exudation is able to infect the roots and cause disease. We also show that the ability of this *P. syringae* strain to block antimicrobial exudation is dependent on the type III secretory system.

Recent work has shown that the Gram-negative bacterial pathogen *P. syringae* pv. *tomato* strain DC3000 (*Pst* DC3000) infects and colonizes *A. thaliana* roots, causing extensive necrosis and ultimately killing the plants[3]. In contrast, seven other *P. syringae* strains that were tested (*P. syringae* pv. *phaseolicola* strains NPS3121 and race 6 (*Psp* NPS3121 and *Psp* rc6), *P. syringae* pv. *glycinea* strain A29-2 race 4 (*Psg* A29-2), *P. syringae* pv. *syringae* strain B728a (*Pss* B728a) and *P. syringae* pv. *maculicola* strains ES4326, M_1 and M_4 (*Psm* ES4326, *Psm* M_1 and *Psm* M_4)) did not cause significant root necrosis or plant mortality when inoculated into liquid medium (Fig. 1a and Supplementary Fig. S1) or sterilized planting mix (Figs 1b and 2a, and Supplementary Figs S2A and S3A) in which *Arabidopsis* seedlings were growing. The seven non-pathogenic *P. syringae* strains also colonized *Arabidopsis* roots relatively poorly compared with *Pst* DC3000 (Fig. 2b and Supplementary Figs S3B and S4). One of the non-pathogenic strains, *Psp* NPS3121, has previously been described as an *Arabidopsis* 'non-host' pathogen