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Evidence and Implications of Mortality Associated with Acute *Plasmodium vivax* Malaria

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SUMMARY

Vivax malaria threatens patients despite relatively low-grade parasitemias in peripheral blood. The tenet of death as a rare outcome, derived from antiquated and flawed clinical classifications, disregarded key clinical evidence, including (i) high rates of mortality in neurosyphilis patients treated with vivax malaria; (ii) significant mortality from zones of endemicity; and (iii) the physiological threat inherent in repeated, very severe paroxysms in any patient, healthy or otherwise. The very well-documented course of this infection, with the exception of parasitemia, carries all of the attributes of "perniciousness" historically linked to falciparum malaria, including severe disease and fatal outcomes. A systematic analysis of the parasite biomass in severely ill patients that includes blood, marrow, and spleen may ultimately explain this historic misunderstanding. Regardless of how this parasite is pernicious, recent data demonstrate that the infection comes with a significant burden of morbidity and associated mortality. The extraordinary burden of malaria is not heavily weighted upon any single continent by a single species of parasite—it is a complex problem for the entire endemic world, and both species are of fundamental

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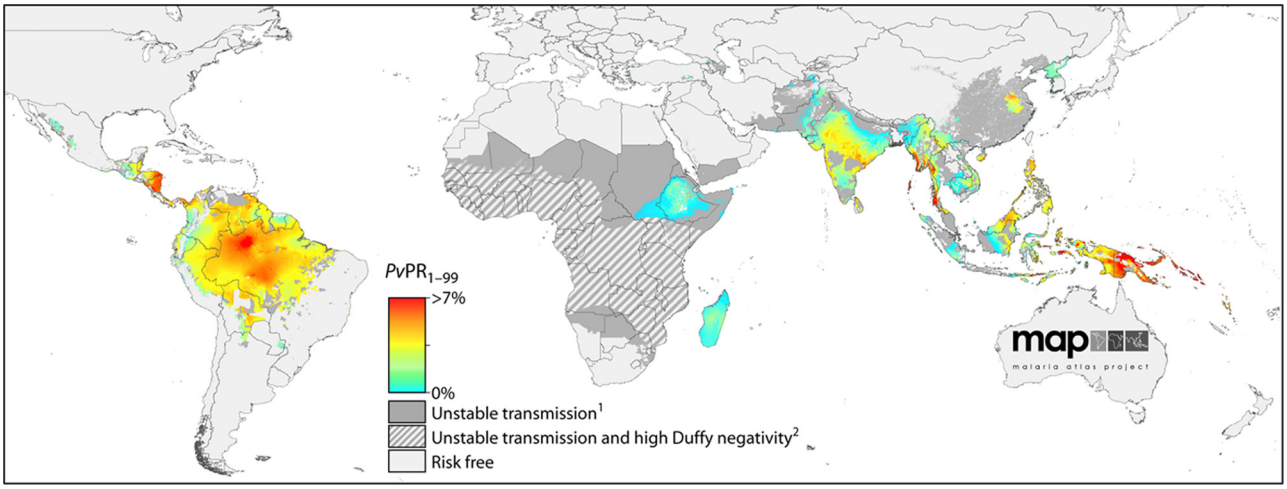

FIG 1 Global map illustrating prevalence of *Plasmodium vivax* in 2010. (Reproduced from reference 5, which was published under a Creative Commons license.)

importance. Humanity must rally substantial resources, intellect, and energy to counter this daunting but profound threat.

INTRODUCTION

Malaria caused by *Plasmodium vivax* seriously challenges human health, attacking 100 to 400 million people each year among the 2.5 billion living at endemic risk (1, 2). The other important cause of malaria, *Plasmodium falciparum*, involves essentially similar global burden estimates (3, 4). The three other species causing human malaria—*Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi* (a zoonosis)—are much less common. The geographic distributions of the two numerically dominant species are largely sympatric, with two important exceptions: (i) endemic *P. vivax* occurs with an extremely low prevalence throughout much of the continent of Africa, as a consequence of human genetic negativity for Duffy factor surface molecules required for invasion of red blood cells (RBC) (5–7); and (ii) *P. vivax* occurs at subtropical and temperate latitudes that are inhospitable to *P. falciparum*, such as the Korean Peninsula, China, and southwestern Asia. The center of weight of the burden of *P. falciparum* is Africa, whereas that for *P. vivax* is Asia, especially South and Southeast Asia (3). Although relatively few people live at risk in the Americas, endemic transmission dominated by *P. vivax* is widespread throughout Central and South America (5) (Fig. 1).

Despite the availability of evidence suggesting otherwise (1–4, 8–10), contemporary media, expert reports, and technical articles published in peer-reviewed journals often express statements much like these: "More than 90% of world's malaria burden is in Africa" (11) or ". . .with Africa having more than 90% of this burden" (12). The July 2007 *National Geographic* carried on its cover a dramatic portrait of a mosquito and the bold title "Malaria: Stopping a Global Killer" (13). That otherwise superb article failed to mention *P. vivax*, but in so doing it faithfully represented the dominant expert opinion that *P. vivax* is clinically benign and its burden a relatively unimportant piece of the global malaria problem. Indeed, an audit of investments in malaria research and development showed that *P. vivax* accounted for 3.1% of global spending during 2007 to 2009 (14). The problem extends beyond research and development: a historic $1.2 billion initiative launched in 2005 by the U.S. government, the President's Malaria Initiative, strictly limited assistance to nations on the continent of Africa. Snow and colleagues (15) quantified inequities in international donor assistance for the malarious nations in Asia, concluding that ". . .countries where *P. vivax* continues to pose threats to control ambitions are not as well funded." Piggot et al. (16) estimated that per capita spending for malaria control by population at risk was $1.60 for Africa versus $0.33 in Central and Southeast Asia. The perception of *P. falciparum*, and therefore Africa, as dominating the global malaria burden carries very significant consequences with respect to the response of humanity to that problem.

Perhaps the most striking and potentially dangerous of those many consequences may be appreciated by consideration of the chemotherapy against dormant forms of *P. vivax* in the liver (called hypnozoites). These parasites cause multiple clinical attacks over the months (up to approximately 2 years) following a single infectious bite by the anopheline mosquito vector. No such forms occur in falciparum malaria—a single infectious bite causes a single attack within about 2 weeks. The only drug available for preventing the recurrent attacks, also called relapses, is primaquine. That drug has been in continuous use for over 60 years, but this extraordinary longevity should not be misconstrued as lasting suitability: primaquine is a seriously flawed drug, causing a mild to severe acute hemolytic anemia in patients with an inborn deficiency of glucose-6-phosphate dehydrogenase (G6PDd). This highly diverse and complex X-linked disorder affects approximately 500 million people, most of them living in regions where malaria is endemic and where the prevalence of G6PDd averages 8% (17, 18). Diagnosis of G6PDd requires a laboratory capacity that is largely absent in areas where most malaria patients live, and inadvertent dosing of G6PDd patients with primaquine can lead to serious hemolytic anemia and even death (19, 20). In treating an infection considered relatively benign, most providers rationally opt against a therapy incurring significant risk of such severe adverse effects. Prolonged dosing (14 days) and scant contemporary evidence demonstrating efficacy (21–23) exacerbate avoidance of primaquine therapy. The hypnozoite reservoir of *P. vivax* goes effectively unchallenged due to the significant danger and operational inadequacy of primaquine. In zones of endemicity,

this drug is not fit for its purpose as currently prescribed. The failure of several generations of malariologists to address this problem stems from the conviction that *P. vivax* rarely causes life-threatening disease.

If the burden of *P. vivax* in Asia and the Americas were discovered to carry a substantial risk of mortality, then the energies in dealing with this species would likely take on a more substantial character. In the meantime, however, the conventional view of vivax malaria as generally harmless prevails. Wikipedia (accessed 8 September 2012), for example, explained on its page for malaria, "The vast majority of deaths are caused by *P. falciparum* while *P. vivax*, *P. ovale*, and *P. malariae* cause a generally milder form of malaria that is rarely fatal." S. F. Kitchen perhaps best expressed that view, and more authoritatively, in the influential text of malariology published by Boyd in 1949 (24): "As a general rule vivax infections exhibit relatively benign characteristics. Observations of the pathogenic tendencies of numerous immunologically distinct strains in a large number of induced attacks causes one to believe that instances of death (of otherwise healthy adults) due to infection by this parasite alone must indeed be rare."

The Boyd textbook captured what may be considered the apex of expertise in malariology during the past century, profoundly influencing the field in that era and the present. This review critically examines the sentiment expressed by Kitchen, on the basis of both evidence contemporary to it and a large body of newer evidence regarding the capacity of infection by *P. vivax* to provoke complications leading to serious illness and death.

(The work represented in this review was presented at the Gordon Conference on Malaria in Tuscany, Italy, in August 2011.)

UNCERTAINTY IN GLOBAL MALARIA MORTALITY DATA

The primary weakness in the assertion that *P. falciparum* causes almost all global mortality due to malaria, and therefore that *P. vivax* causes virtually none, is the paucity of credible evidence for species-specific mortality rates in zones of endemicity. Data from India and Indonesia illustrate the extraordinary difficulty and uncertainty in estimating mortality caused by any species. In 2010, Dhingra et al. (25) reported findings from a large study of mortality in India surveying 122,000 deaths by verbal autopsy. Despite an estimate from the World Health Organization (WHO) of 15,000 (95% confidence interval [95% CI] = 9,600 to 21,000) deaths due to malaria in that country each year (26), Dhingra et al. estimated 205,000 deaths (95% CI = 125,000 to 277,000 deaths). Hay and colleagues (8) estimated 102 million (95% CI = 31 to 187 million) clinical attacks caused by *P. falciparum* alone in that nation, whereas the WHO estimate for clinical attacks caused by any species was less than one-third the lower limit of that confidence interval (27). Similarly wide discrepancies appear in Indonesia, where the WHO estimated approximately 2 million cases of malaria per year, with several thousand deaths (28). The Malaria Atlas Project estimated 12 million cases of *P. falciparum* alone in 2009 (29), and *P. vivax* (disease burden estimates not yet available) represents nearly half of cases in cross-sectional surveys (28). The Central Bureau of Statistics for Indonesia conducted national household health surveys in 1995 and 2001, and each estimated 15 to 30 million clinical cases of malaria, causing 30,000 to 38,000 deaths (28).

These examples of widely divergent malaria morbidity and mortality estimates in India and Indonesia—relatively well-resourced nations compared to others with endemic malaria—demonstrate the great depth of uncertainty. The true burden of disease and death imposed by malaria in general, much less a particular species, cannot now be reported confidently at the national or global level. The recent study of global malaria mortality of Murray et al. (30) illustrates this problem. These investigators limited the analysis of vivax malaria mortality to 15 unidentified nations having only that species present. The Malaria Atlas Project (Peter Gething, personal communication) identified 14 nations of endemicity having only *P. vivax*: the sum of at-risk populations among them accounted for 0.81% of the global population at risk, and extremely low estimates for "pure" vivax malaria mortality emerged. The authors cautiously and appropriately pointed out that they could not disaggregate mortality caused by *P. vivax* for the nations also having endemic *P. falciparum* malaria, i.e., those representing >99% of the total population at risk for *P. vivax* infection. Global malaria mortality estimates from any source offer no evidence of species composition—attribution to *P. falciparum* rests solely upon the presumption of death as a very rare outcome of *P. vivax* infection.

Relatively weak evidence supports the notion that *P. falciparum* in Africa overwhelmingly dominates the global burden of malaria. The entrenched benign-malignant dichotomy of the two species accounts for the conviction of that perception despite such epidemiologic weakness. In fact, both species in most settings of endemicity mostly cause an asymptomatic or mild illness (31–33), and each could thus be characterized as typically relatively benign. The evidence reviewed below suggests that the converse may also be true, i.e., both species appear to be associated with serious illness and death and could sometimes be seen as malignant. The most probable and more complex reality of the clinical manifestations of these infections in zones of endemicity defies a simplistic stereotype of benign versus malignant infection. The factors in settings of endemicity—host or parasite genetics, immunity, or demographic and socioeconomic determinants—that cause a normally benign course of any *Plasmodium* species to turn deadly remain largely unknown.

The study of mortality in India (25) estimated that 86% of deaths occurred away from treatment centers, in areas where diagnosis, reporting, and analysis are challenging and unlikely. However, even when patients do become severely ill and hospitalized, assigning responsibility to either species is fraught with diagnostic and clinical uncertainty. A malignant versus benign diagnostic taxonomy likely comes into play, and individual patients suffering severe and fatal malaria may be presumed to have falciparum malaria. The practice of mingling clinical course and consequence with taxonomic identity among the plasmodia is deeply rooted in the scientific history and dogma that surrounds malaria. Since the benign-malignant dichotomy of *P. vivax* versus *P. falciparum* effectively defines how the global malaria problem is perceived and managed, the historic evidence underpinning that dichotomy is clearly crucial in the rational conception of future strategies to be arrayed against that problem.

ORIGINS OF THE BENIGN-MALIGNANT DICHOTOMY

Clinical "Taxonomy" of the Malarias

The prominent U.S. Army surgeon George Sternberg published the medical textbook *Malaria and Malarial Diseases* in 1884 (34). Only 4 years earlier, Alphonse Laveran, a French Army doctor, had described the protozoan etiology of malaria (35), in a report

TABLE 1 Nomenclature of the human malarias

Zoological nomenclature	Antiquated clinical nomenclature	Obsolete clinical nomenclature	Accepted clinical nomenclature	Prognostic clinical identity
Plasmodium vivax	Remittent or intermittent quotidian or tertian malaria	Benign tertian malaria	Vivax malaria	Acute pernicious[a]
Plasmodium falciparum	Remittent or intermittent quotidian or tertian malaria	Malignant tertian malaria	Falciparum malaria	Acute pernicious
Plasmodium malariae	Quartan intermittent malaria	Quartan malaria	Malariae malaria	Chronic pernicious[b]
Plasmodium ovale[c]	Remittent or intermittent quotidian or tertian malaria	Benign tertian malaria	Ovale malaria	Unknown but possibly acute pernicious
Plasmodium knowlesi	None[d]	None	Knowlesi malaria	Acute pernicious

[a] Recommended here, not yet accepted and applied.
[b] Causes irreversible kidney damage or splenomegaly with some chronic infection states.
[c] Described in the 1920s; it was synonymous with *P. vivax* up to that time.
[d] Not known as a human malaria until 2004, when it was confirmed as a zoonosis from macaques in Southeast Asia.

met with stubborn and unjustified skepticism from imminent malariologists of the day (36). Sternberg briefly refers to Laveran's discovery as a hypothesis, among several others he considers as possible causes of malaria. Sternberg defined malaria this way: "An unknown poison, of telluric origin, the cause of periodic fevers." The "telluric origin," one may suppose today, affirmed natural earthly causes as opposed to vaporous miasmas, accounting for the term. His definition offers little other clarity. Sternberg's text thus provides insights into the complex clinical classification schemes assigned to the various manifestations of the malarias free of biases linked to species identity.

Malariologists of that age certainly understood that distinct diseases were at work with malaria. Sternberg confidently lays out their division (34), writing that ". . . periodicity is not peculiar to malarial fevers. Nevertheless, the periodic fevers, under which title we include the various types of intermittent and of remittent fevers, are so well defined as a class and so widely known that there is no ambiguity in our definition."

As shall be seen, the discovery of the plasmodia and their species identities did not buttress this confidence. On the contrary, species identity decisively informed the rational necessity of wholly discarding these classifications, whether heeded or not. Table 1 summarizes the past and present nomenclature of the malarias.

Clinicians of the 1880s classified malaria fevers broadly, as remittent or intermittent (quotidian, tertian, or quartan). These practical class definitions were relatively simple and straightforward, but many variants occurred with each, according to conspicuous or subtle clinical features. For example, "congestive intermittent" malaria bore the clinical hallmarks and poor prognosis (Table 2) of the cerebral malaria often caused by *P. falciparum*. Each class had well-known prognoses ranging from very rarely to very often fatal, which thus guided clinical management. A key ambiguity appeared between remittent and quotidian intermittent malarias. This posed a significant clinical problem because these classes had case fatality rates of 13 to 34 and 1 per thousand cases, respectively (Table 2). Sternberg complained of them (34), "The dividing line between quotidian intermittent and simple remittent is an arbitrary one, for they are in fact but different forms of the same disease and often pass insensibly one into the other."

Intermittent fevers had afebrile intervals, whereas remittent high fevers had moderately febrile intervals, and both *P. falciparum* and *P. vivax* can exhibit both patterns in the same patients. As for periodicity, today we also understand that *P. falciparum* and *P. vivax*, despite each having 48-h cycles of asexual reproduction (tertian) linked to febrile paroxysm, typically cause daily (quotidian) paroxysms. Afebrile intervals and the classical tertian fever cycle require relatively well-synchronized parasite populations in the blood and are exceptional except where immunity dampens parasitemia. This perhaps explains in part the good prognosis with the tertian form of intermittency.

Despite the malignant versus benign clinical identities ultimately attached to *P. falciparum* and *P. vivax*, assigning them to remittent (malignant) versus quotidian or tertian intermittent (benign) clinical identities was not possible. Both species regularly cause these patterns, and each could therefore be represented among the cases and fatalities ascribed to these malarias in American soldiers during the Civil War (Table 2).

Clinical versus Species Identities

Italian scientists taxonomically described the three principal human malaria parasite species, *P. falciparum*, *P. vivax*, and *P. malariae*, in the 1890s (35). Scientists and clinical investigators set out to reconcile the standard clinical classification scheme to these

TABLE 2 Malaria among Union soldiers in the American Civil War, 1861–1865[a]

Group and malarial disease	No. of cases	No. of deaths	No. of fatalities/ 1,000 cases
Caucasian troops (2,269,793 man-years from 1861 to 1865)			
Remittent	270,365	3,591	13.3
Quotidian intermittent	410,713	420	1.0
Tertian intermittent	345,471	354	1.0
Quartan intermittent	38,705	83	2.1
Congestive intermittent	12,824	3,139	245
Total	1,078,078	7,587	7.0
African-American troops (134,367 man-years from 1863 to 1866)			
Remittent	21,083	717	34.0
Quotidian intermittent	42,035	47	1.1
Tertian intermittent	32,038	42	1.3
Quartan intermittent	2,876	13	4.5
Congestive intermittent	1,987	662	333
Total	100,019	1,481	14.8

[a] Adapted from the 1884 work of Sternberg (34).

new species identities. That scheme was deeply entrenched as standard practice during this era, and even as late as the 1940s, expert malariologists were still using the clinical classification terminology from Sternberg's time. In the 1949 text by Boyd (24), Kitchen describes *P. falciparum* fevers (see Fig. 290 in reference24) as "initial remittency followed by quotidian intermittency in falciparum malaria primary attack." He uses the same terms to describe the same fever patterns in *P. vivax* (see Fig. 299 in reference24). Kitchen explains elsewhere in the text, "As a group designation, the term 'remittent fever' is not particularly apt, and it is used here to avoid confusion." He dismisses the clinical terminology as follows: "Such distinctions are unimportant, and in any case intricate classifications based on febrile patterns are fallacious." Kitchen also discusses the work of the post-Laveran malariologists seeking to unify species identity with what was, to them, a useful clinical diagnostic framework. He wrote (24) that "clinical observations were particularly stressed, and efforts were made to adapt parasitologic findings to them rather than to interpret the former in light of the latter."

This is a key observation and indictment of the investigators who first followed up on Laveran's historic finding. Clinical manifestations remained the primary tool for classifying the human malarias, with species identity taking secondary consideration. As Kitchen pointed out, logic and reason demanded the inverse approach. He cites the early work of Osler, Marchiafava, Bignami, Mannaberg, Thayer, Hewetson, and James, although flawed in that respect, as having laid the foundations of taxonomic order in the clinic and the emerging reality of great variation in course and consequence within species. Despite such progress, the terms "malignant" and "benign" for *P. falciparum* and *P. vivax*, respectively, emerged into common use. As early as 1901, the pathologist J. Ewing (37) challenged the characterization of *P. vivax* as benign by detailing the autopsy of a fulminant case in New York City. He wrote, "While the statement of the Italian authorities has long held true that no autopsy has been reported in a case of malaria with the large tertian parasite [*P. vivax*], as the infection is never fatal, the present case requires modification of this view."

Only 10 years after the description of *P. vivax* as a species, its identity as benign was apparently already considered firmly established. Play of the clinically useful classifications in this designation, rather than a systematic and objective survey of mortality, appears to have been a dominant consideration.

Notwithstanding authoritative recommendations against clinical designations for taxonomic purposes over 60 years ago (38, 39), the terminology of "benign tertian malaria" and "malignant tertian malaria" for these two species stubbornly persists up to the present day. Mingling taxonomic identity and clinical classifications is inherently flawed and, as history now instructs, dangerously misleading with respect to vivax malaria. When the practice of malaria therapy for tertiary syphilis flourished in the 1920s and 1930s, the "benign" identity led providers to choose *P. vivax* as the overwhelmingly favored agent of therapy.

VIVAX MALARIA KILLED NEUROSYPHILIS PATIENTS

Therapeutic Paroxysm

Wagner-Jauregg became the 1927 Nobel laureate for his discovery in 1917 that acute malaria cured neurosyphilis, an otherwise invariably fatal disease, in some patients. The inspired hope of that life-saving therapy may be compared to the discovery of antiretroviral therapies for people living with human immunodeficiency virus today. However, the efficacy of malaria therapy under the best conditions was only about 30% (40, 41). The remainder of patients had either no benefit or only brief improvements. "Benign" *P. vivax* consistently had relatively low and seemingly less-threatening parasitemias but nonetheless provoked the paroxysms underpinning the treatment (42). The severity and frequency of these correlated with the probability of treatment success, with severe malaria thus being the intent and instrument of therapy. The many intense daily paroxysms with rigors (about a dozen was a typical course of treatment [43]) (Fig. 2) proved extremely physically punishing, and data from that era reveal an exceedingly dangerous therapeutic enterprise. Nicol explained the physician's ethical calculus (44): "Risks, however, must be taken in treating a disease, which if untreated, proves fatal."

An Often Lethal Therapy

According to Fong (45), the earliest attempts at malaria therapy in the United States killed approximately 20% of patients. Martin (46) reported that during the first 5 years of malaria therapy in the United Kingdom, among 1,597 patients treated, 541 (34%) died in the course of treatment or soon thereafter. Providers of the treatment quickly learned to exclude patients with comorbidities as unlikely to survive. They became more expert at the clinical management of acute malaria—administration of subcurative doses of quinine, for example, dramatically improved case fatality rates and became standard practice (47). As the therapy matured, investigators reported what amounted to optimized rates of death with the treatment. In Denmark, for example, 13% of patients died among 100 treated in a 1930 series, whereas a decade later 7% of a series of 579 patients died in treatment (M. Lomholdt [cited in reference 48]). Although optimized, the treatment still required multiple bouts of inadequately treated acute malaria, and reports typically described 5 to 15% treatment fatality rates in American and European treatment facilities applying *P. vivax* (Table 3) (41, 43, 45–47, 49–55; J. P. Verhave, submitted for publication). Most deaths occurred after the sixth paroxysm (45). Nicol described the optimized treatment fatality rate with the Madagascar strain of *P. vivax*—a notoriously virulent strain with relatively good efficacy against neurosyphilis—as typically 10 to 15% for patients in the United Kingdom (42, 56). In contrast, James et al. (57) described their experience with more than 50 induced *P. falciparum* infections in syphilis patients in the same clinics in the United Kingdom as carrying what they considered a typical 4% treatment fatality rate for that species. The irony of this observation was not lost on them—they referred to *P. vivax* and *P. falciparum* as "so-called benign" and "so-called malignant," respectively.

Parasite Virulence or Patient Vulnerability?

The providers of malaria therapy naturally sought to understand the causes and risk factors for a fatal outcome. In one series of 34 deaths at a single hospital (St. Elizabeth's in Washington, DC) (45), autopsies of 17 people listed the following causes of death: "acute malaria" (8 cases), "myocardial failure" (7 cases), "pulmonary thrombosis" (1 case), and "tuberculosis bronchopneumonia" (1 case). Fong (45) described the nonautopsied causes of death in that series as follows: "myocardial degeneration accounted for 7; there were 2 nephritic deaths, 7 pulmonary, and 3 cases of acute malaria." Nicol (44), in the United Kingdom, expressed this view on the issue: "One must acknowledge that,

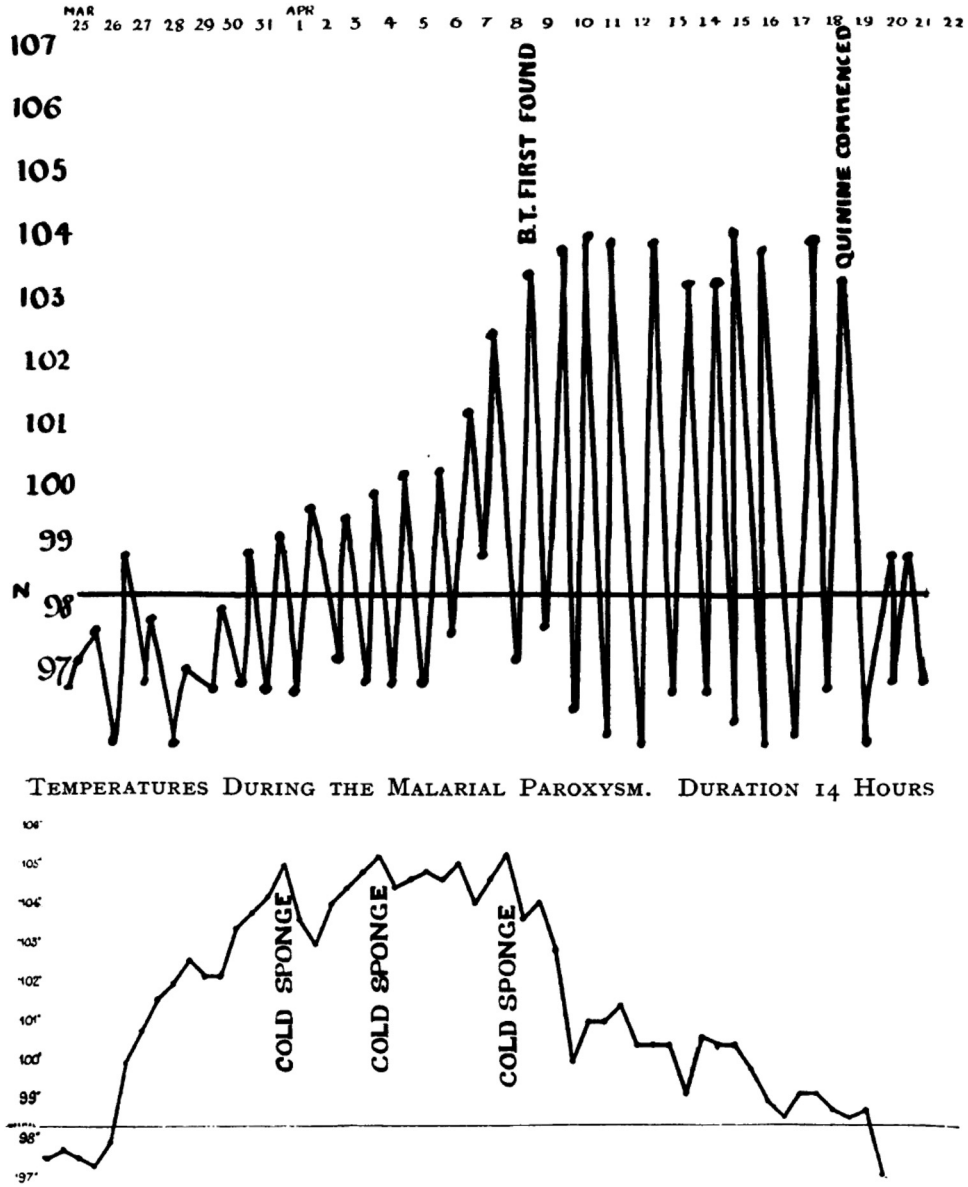

FIG 2 (Top) Typical course of repeated daily paroxysms in a neurosyphilis patient treated with *P. vivax* (body temperature is given in degrees Fahrenheit). (Bottom) Course of a single 14-hour paroxysm. (Reprinted from reference 47 with permission from BMJ Publishing Group Ltd.)

though in a few cases death is caused by intercurrent disease, malaria, if not directly responsible, must be regarded as a contributing factor; in most cases malaria itself is the cause."

The clinical and parasitological course of vivax malaria in neurosyphilis patients was essentially similar to that in otherwise healthy patients—the paroxysms were no more severe, the parasitemias no higher, and the anemia no deeper. Death in most of these patients did not appear related to underlying disease brought about by neurosyphilis or intercurrent diseases that often occurred among middle-aged patients of that era. In the heyday of this treatment during the 1930s, most patients had been diagnosed recently and referred for immediate therapy. The recruitment of seriously ill patients resident in the asylums for neurosyphilis largely ceased with the understanding of their vulnerability to death by this punishing therapy. The majority of deaths accounting for the 5 to 15% treatment mortality seem attributable to an ordinary course of infection by *P. vivax*, uninterrupted by chemotherapy, in relatively healthy patients. If so, the species would appear to be capable of an often-pernicious course.

Other observations point to the same conclusion. Conspicuous differences in strain-specific virulence of *P. vivax* in these patients became well known. The most dramatic illustration of this comes from the experience in the Netherlands. At first, patients were treated with strains of *P. vivax* endemic to that nation in that era. None of these patients died under treatment (Verhave, submitted), but the efficacy against neurosyphilis was relatively poor. Dutch providers switched to the so-called Madagascar strain of *P. vivax* (it likely originated elsewhere [58]) because it came with relatively high rates of treatment success. The 8% fatality rate with treatment by that strain in Holland (Verhave, submitted) presum-

TABLE 3 Mortality during or soon following treatment of neurosyphilis with *Plasmodium vivax* (1920s and 1930s)

Clinic	Strain	No. of patients treated	No. (%) of patients who died	Reference
St. Elizabeth, Washington, DC	St. Elizabeth	1,012	34 (3.4)	45
Mayo Clinic, USA	St. Elizabeth	100	5(5.0)	49
Mayo Clinic, USA	St. Elizabeth	984	24 (2.4)	49
Cleveland City Hospital, USA	Not specified	580	74 (13)	50
King's Park Hospital, NY, USA	Not specified	100	8 (8.0)	51
Survey of many clinics, USA	Various and not specified	8,354	448 (5.4)	52
Whittington County Mental Hospital, UK	Not specified	225	29 (13)	53
Hanwell Mental Hospital, UK	Not specified	36	3 (8)	54
Meagher Report, UK	Not specified	1,532	135 (9)	55
Caldwell Report, UK	Not specified	579	63(11)	41
Winnick Mental Hospital, UK	Not specified	245	67 (27)	46
Horton Mental Hospital, UK	Madagascar	376	52(14)	43
Various clinics, Netherlands	Madagascar	807	62 (7.7)	Verhave, submitted

ably saved more lives from neurosyphilis than were lost to its therapy with vivax malaria. The strain-specific mortality risk points to the parasite rather than the patient as the basis of a fatal outcome.

ENDEMIC VIVAX MALARIA KILLED PATIENTS

Endemic malaria still occurred across much of the rural southern United States during the 1930s. Dauer and the preeminent parasitologist of that era, E. Carroll Faust of Tulane University, conducted a rare retrospective study of malaria mortality by species (59). States where malaria was endemic were approached and assessed, but only two could offer analyzable data and specimens, with the most thorough obtained from Mississippi. In 1935, the malaria death rate in that state was 26/100,000 population, approximately that for automobile fatalities in the United States today. Among deaths in Caucasians, 35% had confirmed antemortem blood film examinations, with 33%, 13%, and 4% of cases being reported as *P. falciparum*, *P. vivax*, and *P. malariae* infections, respectively. The balance of the sample was not analyzable. Among African-Americans, 29% came with antemortem blood film examinations, with 21%, 22%, and 2% prevalences of the same respective species. The only other state to provide useful data to Dauer and Faust was Florida, which reported 40%, 21%, and 2.5% of deaths attributed to malaria caused by *P. falciparum*, *P. vivax*, and *P. malariae*, respectively. Thus, according to those state health authorities, vivax malaria often caused death in the areas of endemicity in the United States in the 1930s.

Prokopenko (60) summarized 900 cases of "fulminant *P. vivax* malaria" reported from the Soviet Union between 1935 and 1947. The occurrence of life-threatening complications was encountered so commonly that its epidemiology is the subject of Prokopenko's analysis, e.g., the majority of cases were in children of 2 to 5 years of age and occurred early in the year (relapses), whereas adult cases tended to appear later in the year (primary infections). Significant delays in treatment occurred in most cases of death. Although vivax malaria persisted in the Soviet Union, Prokopenko reported the disappearance of endemic fulminant vivax malaria in 1953, with the implementation of eradication programs, i.e., radically improved diagnosis and treatment services, including hypnozoitocidal therapy in the form of quinocide, a Russian 8-aminoquinoline differing from primaquine only in the position of the methyl group on the alkyl side chain (61).

Endemic vivax malaria in other settings indeed sometimes appears to be very rarely threatening. A steep epidemic of vivax malaria in the Netherlands occurred during 1943 to 1946, and the superb malariologist Swellengrebel described mortality due to this illness as "practically non-existent" (62). The relatively mild and nonthreatening course of illness typical of the Dutch strains of *P. vivax* was already well known from the experience with malaria therapy of neurosyphilis in that country. More recently, Luxemburger and colleagues (63), working in Thailand in the 1990s, found no fatalities among 2,573 documented cases of vivax malaria, whereas 5% of 5,776 patients with falciparum malaria did not survive. These findings, in a population described as having access to good clinical care for malaria, may be a consequence of either local occurrence of a relatively nonthreatening strain (as in Holland) or access to good care (as in Russia). Vivax malaria progressing to threatening disease may require a virulent strain, negligent management, or both. The prognosis may be somewhat better with good care of *P. vivax* than the case with *P. falciparum*, but this by no means implies an intrinsically benign character of most strains.

The data from areas of endemicity in the United States and from the Soviet Union, along with others (64–67), demonstrated that lethality associated with a diagnosis of *P. vivax* malaria was not a phenomenon restricted to neurosyphilis patients. Kitchen was certainly aware of this—and the well-documented mortality in neurosyphilis patients—in 1949, when he described *P. vivax* as an intrinsically benign species of parasite. How he reconciled that conclusion to mortality in zones of endemicity and in neurosyphilis patients is a vitally important question today.

WHY "BENIGN" VIVAX MALARIA?

Experimental Setting

Kitchen's expertise with malaria derived from his long experience in treating neurosyphilis in Tallahassee, FL. The therapy evolved into what Kitchen characterized as "a renaissance in clinical malariology." Kitchen considered the careful, systematic study of these infections to be the foundations of modern clinical malariology, "for it has contributed immeasurably. . .to our systematic knowledge concerning the natural evolution of these infections." He contrasted this well-controlled setting with the real world as follows (24): "Until 2 decades ago the physician practicing medicine in the endemic areas was practically our only source of information concerning clinical malariology. While his contributions have been indispensable, as an observer he has labored simultaneously under the advantage of being exposed to a unique variety of events in the course of plasmodial infections, and the disadvantage of being permitted to study but a small segment of each infection."

Kitchen seems to express a superior command of scientific

ground truth in the setting of his experience with therapy of neurosyphilis. Observations from practice in the field came with inherent limitations and important confounders. He dealt with the many published reports of serious illness with a diagnosis of *P. vivax* infection as follows (24): "Although the causation of pernicious attacks is generally attributed to *P. falciparum*, some authors (James 1922; Hehir 1927) state that serious conditions are also encountered in the other plasmodial infections. While inter-strain differences seem to exist with reference to the virulence of *P. vivax*, this parasite does not appear to possess, in the sense that *P. falciparum* does, any attributes that induce perniciousness. It is therefore difficult to understand how it can, in the absence of contributory factors, cause dangerous clinical states."

Kitchen's opinion is clear: absent the sullying effects of other infections and underlying disease, *P. vivax* did not threaten patients. He added, "It is not the writer's intention to deny categorically that this parasite can do so; it is felt, however, that in view of known characteristics of *P. vivax* that have been studied in a great many cases under controlled conditions, great caution should be exercised in ascribing pernicious events to this *Plasmodium* alone."

Kitchen discusses a number of reports of severe illness with a diagnosis of *P. vivax* infection from zones of endemicity and generally dismisses each in turn. He summarizes that discussion as follows: "Whether these unusual conditions should be considered as manifestations or as complications of vivax malaria does not, of course, evade the fact that they apparently occur in the described circumstances and thereby provide diagnostic difficulties."

This expresses both his confidence in the certainty of the experimental setting and his deep skepticism for findings not similarly derived. However, Kitchen's view of serious complications with a diagnosis of vivax malaria as "unusual" comes with no supporting epidemiological evidence. Case reports carry no intrinsic measures of relative risk. Whether the conditions he refers to were "unusual" or "ordinary" evades credible characterization of risk in a statistical sense. Such assessments have only very recently become available (see Current Evidence).

If deaths occurred among the patients Kitchen treated with vivax malaria, no mention could be found of these. Kitchen also does not raise any of the mortality data from therapy of neurosyphilis detailed in this review, yet these also occurred under the "controlled conditions" of his own experimental model. He seems to have considered mortality in neurosyphilis patients somehow extraordinary and not relevant to clinical malariology in other patients. This seems remarkable, since the parasitological and clinical course in these patients was deemed sufficiently ordinary to characterize it as representative of that in broader patient populations. Kitchen's chapters in the Boyd textbook have been considered the definitive and authoritative description of the courses and consequences of *P. falciparum*, *P. malariae*, and *P. vivax* infections in humans, but the substantial evidence of the course of *P. vivax* often ending in death appears nowhere in those chapters.

Parasitemia and Severity

Whereas Nicol's many contributions to the malaria therapy literature focus on the patient surviving therapy and neurosyphilis, Kitchen's contributions rarely speak of treatment modalities or outcomes. Kitchen focuses on the data from his patients as models of the natural course of infection by malaria parasites uninterrupted by chemotherapy. Although Kitchen certainly describes clinical features in careful detail, the consequences in terms of mortality risk or effects on efficacy against neurosyphilis are rarely subject to description or discussion.

Despite the benign identity Kitchen attached to *P. vivax*, the clinical features he described appear incompatible with that designation. He reported fevers typically ranging between 104°F and 106°F, with fevers exceeding that upper limit (but below 107°F) being quite common. Hyperpyrexia did cause convulsions, but only rarely. Rigor, indicative of a severe paroxysm, occurred in 71% of 713 studied paroxysms. Severe anemia (<5 g/dl) was especially common with acute infections of a month or more. Jaundice was "not uncommon," and splenomegaly was relatively common, as was vomiting to an extent requiring intravenous rehydration (24). Such disease states in settings of endemicity with limited access to relatively poor care would certainly threaten patients.

Kitchen's many references to "perniciousness" appear to refer strictly to the burden of parasites evident in peripheral blood rather than to the clinical condition. He described parasitemia levels of *P. vivax* very rarely exceeding 50,000/μl, and typically ranging around 10,000/μl. In contrast, *P. falciparum* levels in his patients very often exceeded 100,000/μl, and could do so with great rapidity, e.g., 480/μl, 24,050/μl, and 172,980/μl in one patient on days 1, 2, and 4 of patency, respectively. Kitchen noted the ability of *P. falciparum* to indiscriminately invade red blood cells of any age versus the "possibly. . .obligatory" (later confirmed) preference of *P. vivax* for reticulocytes. This difference, malignant replication of *P. falciparum* versus the low and apparently self-limiting replication of *P. vivax* in peripheral blood, seems to be the crux of Kitchen's argument of benign identity for vivax malaria. Kitchen thus effectively extrapolated the correlation between parasite burdens in peripheral blood and perniciousness in falciparum malaria to vivax malaria, which typically achieved levels of parasitemia considered not threatening in falciparum malaria. In addressing the controversy of threatening vivax malaria, however, he wisely conceded (24) that "present knowledge concerning the provocative potentialities of low-grade parasitemias does not permit denial of the possibility that the presence of *Plasmodium* [*vivax*], even in very small numbers, may serve as an incitant of entirely foreign conditions." Despite the implication of confounding diseases in closing, this concession may be proved prescient. The superior ability of *P. vivax* to provoke inflammatory reactions relative to that of *P. falciparum* (parasite for parasite) is well known today (68, 69), and the role of such reactions in severe illness has been examined and appears highly relevant (70–72).

Nullifying Weaknesses of the Term "Benign Vivax Malaria"

The passage from Kitchen quoted in the introduction may be recognized as conservatively expressed. The statement excludes applicability to children or people who are not otherwise healthy (such as neurosyphilis patients), and careful syntax qualifies and constrains certainty, e.g., "as a general rule," "relatively," "tendencies," "causes one to believe," and "this parasite alone." In so doing, this methodic investigator acknowledged the limitations of his experience. Despite such caution, however, Kitchen accepted the evidence from his careful experimental approach as broadly applicable ground truth while rejecting contrary clinical evidence from beyond his own well-controlled experiments.

The silence of Kitchen on the rich mortality data on neurosyphilis patients most plainly illustrates such selectivity. Readers of

Kitchen who know the malaria mortality data from neurosyphilis patients can only presume that Kitchen considered these patients somehow uniquely vulnerable to fatal outcomes rarely suffered by other patients. Despite dissent from esteemed colleagues practicing malaria therapy, such as Nicol, and abundant evidence offering compelling counterargument—ordinary courses in neurosyphilis patients, endemic mortality, strain-specific lethal virulence, and autopsy findings—Kitchen offers no evidence or argument to support his implicit, unstated point of view on mortality of vivax malaria in neurosyphilis patients. Rather than attempt to reconcile those valid observations with the hypothesis of benign identity, he set them aside without explanation. In the absence of evidence of the supposed dominance of comorbidities among the fatalities or a plausible hypothesis linking death by vivax malaria to neurosyphilis, the lethal outcomes of that therapy should be accepted as directly relevant to clinical malariology in broader patient populations.

The chapters by Kitchen describe threatening clinical conditions with acute vivax malaria, but Kitchen concluded that *P. vivax* alone could not threaten otherwise healthy patients. The course he detailed for neurosyphilis patients, with the exemption of lethal outcomes, was nonetheless considered representative of broader patient populations. Kitchen appears unable to have argued the logic and reason of the exemption granted fatal outcomes. He also seems to have been unable to acknowledge the clinical states he described for vivax malaria as intrinsically threatening and dangerous to any patient, with or without neurosyphilis. Those clinical states certainly threatened patients and very probably, as Nicol surmised (44) and autopsy findings indicated (45), directly caused death in many of them.

The evidence underpinning Kitchen's characterization of *P. vivax* as benign seems to rest upon the parasitemias of *P. vivax* contrasted with those of *P. falciparum*. In other words, he presumed that the low and self-limiting numbers of parasites in peripheral blood were insufficient to cause serious threat. Here Kitchen provides a plausible and testable hypothesis: if serious illness occurs in patients with a diagnosis of vivax malaria and comorbidities may reasonably be excluded, then the hypothesis cannot stand. Recent data from across the vast expanse of endemic vivax malaria affirm that *P. vivax* is very often associated with severe illness and risk of death with relatively low levels of parasitemia. These risks approximate those in patients with a primary diagnosis of falciparum malaria and relatively heavy parasite burdens in peripheral blood.

CURRENT EVIDENCE

Case Reports

Table 4 lists 48 published case reports of what the authors considered extraordinary presentations of vivax malaria in their patients from 1990 until the present day. Many of these were identified by searching "*Plasmodium vivax*, severe, fatal" at PubMed (www.ncbi.nlm.nih.gov/pubmed; accessed 12 September 2012), but others were gleaned only from a careful read of the contemporary literature of hospital-based studies reported from zones of endemicity. This table and others in this review exclude reports of illness due to rupture or infarct of the spleen, because this rare and dangerous syndrome is already well known for vivax malaria. Some of these cases do not seem especially remarkable or clinically threatening, but many do, despite only three ending in death. A profound bias against providers publishing fatal outcomes in their patients may be at work: case reports offer almost no insight on relative or absolute risk of poor outcomes. In a statistical sense, rather than being a sample of 48, these cases represent 48 single patient samples. Case reports do not compose a systematic, unbiased sample of disease states associated with vivax malaria. Another key weakness in these data, apart from the relatively small numbers represented, is the absence of a uniform and validated definition of severe malaria based upon statistical linkage with risk of a poor outcome. Such analyses shaped the criteria for classifying falciparum malaria as severe. Until the same is accomplished with vivax malaria, the states of relatively severe disease found in these case reports remain speculative with respect to measured risks of death.

These reports (73–109) at least provide an empirical view of the geographic, demographic, and clinical spectra of severe disease states associated with a primary diagnosis of vivax malaria. The reports represent most of the geographic distribution of *P. vivax*. All ages are represented, and no sex seems to predominate. Both travelers and residents of zones of endemicity are described. Diagnostic certainty ranges from poor to unambiguous. A wide range of syndromes appears, with the exception of the near absence of severe malarial anemia (SMA). Acute respiratory distress syndrome (ARDS), cerebral syndromes (seizures or coma), severe thrombocytopenia, hemorrhage, and shock syndromes are all described for many patients. Most of the reports failed to give quantitative measures of parasitemia, instead empirically describing ordinary or moderate numbers of parasites in peripheral blood films. For the minority of patients with hyperparasitemia, the authors provided counts (up to 3.0% of RBC infected, or approximately 150,000/μl). Other authors reported far more modest counts of parasitemia (e.g., <5,000/μl). There seems to be no clear correlation between the burden of parasitemia and the severity of illness, at least on the scales of parasitemia typically applied to *P. falciparum*, e.g., >200,000/μl comes with a significant risk of a poor outcome.

Case Series

Table 5 lists evidence from case series (110–119). These represent cases selected by the authors from their clinical experiences. These series do not necessarily represent a systematic survey of severely ill patients with this diagnosis, nor are denominators of risk available. In some instances, the authors selected only patients representing a particular syndrome, to the exclusion of any others. As such, these case series pose the same limitations as the individual case reports with respect to analytical inference on risk.

The two case series describing all cases of severe vivax malaria without regard to a specific syndrome describe findings essentially similar to those among the single case reports. Exceptionally, both series came with PCR confirmation of the diagnosis of *P. vivax* monoinfection across the 28 patients represented, including 3 deaths among them. The other series in Table 5 describe specific syndromes with a diagnosis of *P. vivax* infection, including pulmonary, renal, neonatal, and ophthalmologic complications. Certainly the most compelling set of data among these case series is the 17 autopsies of patients not surviving a primary diagnosis of *P. vivax* malaria in Brazil. This report, from Lacerda and colleagues at Manaus (119), provides an important and very rare pathological assessment of *P. vivax* as the likely or probable immediate cause of death of 13 of those patients. It is a seminal contribution pro-

TABLE 4 Case reports since 1990 of severe and fatal vivax malaria not involving splenic rupture alone

Yr of publication (reference)	Location[g]	Diagnostic method[a]	Parasite density[b]	Patient age (yr)/sex[c]	Falciparum ruled out?	Diagnosis for coinfection?	Syndrome[d]	Therapy[e]	Outcome
1992 (73)	India	M	NR	3/M	No	Yes	CS	CQp	Death
1992 (73)	India	M	NR	2/M	No	Yes	CS	CQp	Recovery
1993 (74)	India, USA	M	NR	64/F	No	Yes	ARDS	CQ, PQ	Recovery
1997 (75)	Pakistan, Spain	M	NR	38/M	No	No	PD	CQ, PQ	Recovery
1997 (76)	Venezuela	M, P	2.8%	28/M	Yes	No	ALI	CQ, PQ	Recovery
1998 (77)	India, USA	M	1.0%	48/F	No	No	ARDS	CQ, PQ	Recovery
1998 (77)	Honduras, USA	M	0.8%	62/M	No	No	ARDS	QN, DX, PQ	Recovery
1999 (78)	Colombia, USA	M, P	5%	32/M	Yes	No	ARDS	QNi, DX, PQ	Recovery
2001 (79)	Papua New Guinea, USA	NR	NR	47/F	NR	NR	ARDS	NR	NR
2002 (80)	Pakistan	M, R, P	NR	60/M	Yes	No	CS	QNi	Recovery
2002 (81)	India	M, R	NR	43/M	Yes	No	ST, Hm	QN	Recovery
2003 (82)	French Guiana, UK	M, R	<1	52/M	Yes	Yes	ARDS	QN, CQ, MV	Recovery
2003 (82)	India, UK	M, R, P	<1	29/M	Yes	Yes	ST, Jd	CQ, PQ	Recovery
2004 (83)	Afghanistan, USA	M, P	0.3–0.8%	21/M	Yes	No	ARDS	QN, MV	Recovery
2004 (84)	Indonesia, Singapore	M, R	0.65% (mixed)	48/F	Mix	Yes	ARDS, RF, SRm, MAc	QN, DX, MV	Death
2004 (84)	Indonesia, Singapore	M, R	1.2%	48/NR	Yes	No	PE	QN, DX	Recovery
2005 (85)	Brazil	M, R	NR	43/F	Yes	Yes	ST, ARDS	AR, CQ, PQ	Recovery
2006 (86)	India	M, R	NR	12/M	Yes	No	CS	ARi	Recovery
2006 (86)	India	M, R	NR	12/M	Yes	No	CS	ARi	Recovery
2006 (87)	Turkey	M	0.6%	4/M	No	No	CS	CQ, PQ	Recovery
2006 (88)	Uganda, USA	M, P	1.0%	50/M	Yes	No	PE	QN, DX	Recovery
2007 (89)	Afghanistan, USA	M, P	NR	21/M	Yes	Yes	ARDS, SR	QNi, DX, SI	Recovery
2007 (90)	South Korea	M, R, P	NR	21/M	Yes	No	SAM	CQ, PQ	Recovery
2007 (90)	South Korea	M, R, P	NR	33/M	Yes	No	SAM	CQ, PQ	Recovery
2007 (91)	Pakistan, UK	M, R, P	3%	59/M	Yes	No	SAM, ARDS	CQ, PQ	Recovery
2007 (92)	India, UK	M, P	0.3%	69/M	Yes	No	ARDS	CQ	Recovery
2007 (93)	India	M, R	<0.1%	28/F	Yes	No	ARDS	ARi	Recovery
2008 (94)	India	M, R	NR	Adult/M	Yes	No	CS	CQ	Recovery
2008 (94)	India	M, R	NR	Adult/M	Yes	No	CS	CQ	Recovery
2008 (94)	India	M, R	NR	Adult/M	Yes	No	CS	CQ	Recovery
2008 (95)	Brazil	M, P	Marrow	14/NR	Yes	No	ST, Sm	CQ, PQ	Recovery
2008 (96)	Afghanistan, USA	M	NR	NR/M	No	No	ARDS	NR	Recovery
2008 (97)	Venezuela	M	2,000	29/M	No	Yes	ST, SAM, HN	CQ, PQ	Recovery
2008 (98)	India, UK	M, R, P	<1.0%	63/M	Yes	No	ALI	QN, CQ, PQ	Recovery
2009 (99)	India	M, R, P	2,800	4/F	Yes	Yes	ST, Hm	ARp, MQ, PQ	Recovery
2009 (100)	India	M, R, P	>120,000	19/F	Yes	Yes	ARDS	CQ	Death
2009 (101)	India	M, R	NR	42/F	Yes	No	ARDS	ARi	Recovery
2009 (102)	India	M, R, P	NR	19/F	Yes	Yes	CS	ARi, QNi	Recovery
2009 (103)	India	M	NR	1/NR	No	No	CS	QNi	Recovery
2009 (103)	India	M	NR	5/NR	No	No	ST, Hm	QNi	Recovery[f]
2009 (104)	South Korea	M, P	NR	27/F	Yes	No	Mc	CQ	Recovery
2010 (105)	India	M, R	NR	42/M	Yes	No	ARDS	CQ, MV	Recovery
2010 (105)	India	M, R	NR	36/M	Yes	No	ARDS	CQ, MV	Recovery
2010 (105)	India	M, R	NR	15/M	Yes	No	ARDS	CQ, MV	Recovery
2010 (106)	Brazil	M	NR	16/M	No	Yes	SRm	ARi, CQ, PQ	Recovery
2010 (107)	India	NR	NR	Child/F	No	No	ST, Hm	NR	NR
2010 (107)	India	NR	NR	Child/F	No	No	ST, Hm	NR	NR
2011 (108)	India	M, R	NR	7/F	Yes	No	AGN	Rx	Recovery
2012 (109)	India	M, R	2%	29/F	Yes	No	AKI		

[a] M, microscopy; R, rapid diagnostic test; P, PCR; NR, no data/not reported.
[b] Reported as % of red blood cells infected or number of parasites/μl of blood.
[c] M, male; F, female.
[d] ARDS, acute respiratory distress syndrome; AGN, acute glomerulonephritis; AKI, acute kidney injury; ALI, acute lung injury; CS, cerebral syndrome (coma or seizures); Hm, hemorrhage; HN, hydronephrosis; Jd, jaundice; MAc, metabolic acidosis; Mc, myocarditis; PD, pulmonary distress; PE, pulmonary edema; RF, renal failure; SAM, shock or algid malaria; Sm, splenomegaly; SR, spleen rupture; SRm, severe rhabdomyolysis; ST, severe thrombocytopenia.
[e] QN(i or p), quinine (intravenous or parenteral); DX, oral doxycycline; CQ(p), chloroquine (parenteral); AR(i or p), an artemisinin (intravenous or parenteral); MQ, mefloquine; PQ, oral primaquine; MV, mechanical ventilation.
[f] Recovery with sequelae.
[g] Where two locations are listed, the first is the site of infection and the second is the site of treatment and reporting.

TABLE 5 Summary of case series of severe vivax malaria[a]

Yr of publication (reference)	Location	Case selection	No. of cases	Ages	Diagnostics	No. of cases with parasitemia of >100,000/μl	Dominant syndromes	No. of fatal cases
2004 (110)	South Korea	Retinal injury	5	22–31 yr	M,P	1	RI	0
2005 (111)	India	All severe, adult	11	17–53 yr	M, R, P	0	CS, ARDS, RF, Jd	2
2008 (112)	Colombia	Neonatal	5	<35 days	M	NR	SMA	0
2009 (113)	India	All severe, adult	40	18–60 yr	M, R, P	0	Jd, RF, SMA, MOD	2
2010 (114)	Iran	ST	11	NR	NR	NR	ST	NR
2010 (115)	Brazil	All severe, all ages	17	1 mo–60 yr	M, P	0	SMA, Jd, RF	1
2011 (116)	India	Pulmonary	4	NR	M, R	NR	SMA, ARDS	4
2012 (117)	India	Kidney injury	9	5 children, 4 adults	M	NR	AKI	NR
2012 (118)	India	Kidney injury	25	NR	M	NR	AKI, RF, CS, SAM, RD, SMA, ARDS	3
2012 (119)	Brazil	Autopsy series	17	8–88 yr	P	NR	LE, SR, ARDS, MOD	13

[a] NR, not reported/no data; M, microscopy; R, rapid diagnostic test; P, PCR; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; CS, cerebral syndrome (coma or seizures); Jd, jaundice; MOD, multiple organ dysfunction; LE, lung edema; RF, renal failure; RI, retinal injury; SMA, severe malarial anemia; SR, spleen rupture; ST, severe thrombocytopenia.

viding key evidence pointing to fatal vivax malaria as not only plausible but also confirmed in these patients.

Retrospective Hospital-Based Studies

Table 6 lists evidence gathered from retrospective hospital-based studies (120–129). The authors of these reports typically surveyed records of admission to hospitals with a primary diagnosis of malaria. They strived to classify patients as having uncomplicated versus complicated and severe malaria on the basis of definitions or algorithms suited to the evidence available in the records of routine care. Although there are certainly limitations, these studies begin to provide denominators for assessment of risk. The definitions vary across studies, but there tend to be consistent references to at least some of the WHO criteria for severe malaria set forth for falciparum malaria, e.g., a Glasgow coma scale score of <12, >2 seizures, severe anemia (<5 or <7 g/dl), severe thrombocytopenia (<50,000/μl), and others were often applied in these studies. Indeed, most studies also analyzed admissions with a diagnosis of *P. falciparum* infection, giving insights into the relative risks of severe illness between the two important species based upon the same clinical parameters.

A key weakness in most of these reports is diagnostic certainty. Setting aside the difficulty of the microscopic diagnosis of malaria caused by mixed infections for even expert microscopists, the quality of such services among hospitals varies a great deal. Some of the studies labored to cross check the diagnosis (as in the 2012 Pakistani study), but most did not. Most of the caretakers applied routine diagnostic methods in ruling out other important causes of febrile illness in their areas, e.g., dengue, typhoid, typhus, Japanese encephalitis, bacteremia, leptospirosis, and others, but the quality of these services must be considered highly variable and often incomplete. One may reasonably expect, however, these obviously important confounding factors to have exerted roughly equal effects among patients having a diagnosis of malaria caused by either species of *Plasmodium*.

These studies examined thousands of admissions with a diagnosis of falciparum or vivax malaria (mixed infections of the two species, which were also reported, are excluded from this and other summaries in this review). The risk of being classified as having severe illness was only slightly higher for falciparum than vivax malaria. Summing the data, where possible, shows 5,996 and

TABLE 6 Summary of retrospective hospital-based studies of severe malaria[a]

Yr of publication (reference)	Location	No. of admissions		No. of severe cases		No. of fatal cases		Diagnostics	Dominant *P. vivax* syndromes
		P. falciparum	*P. vivax*	*P. falciparum*	*P. vivax*	*P. falciparum*	*P. vivax*		
2001 (120)	South Korea	0	101	0	29	0	0	M	ST, SR
2004 (121)	Malaysia	304	386	28	3	10	1	M	NR
2007 (122)	Indonesia	3,967	1,135	330	36	79	9	M	SMA, CS, Jd
2007 (123)	Pakistan	242	270	230 (total for both species)		5	4	M, R	ST, SMA
2009 (124)	India	41	221	NR	29	NR	3	M, R	ST, HD, RD, ARDS
2009 (125)	Venezuela	1	17	1	7	1	1	M	SMA, Jd
2012 (126)	Brazil	NR	NR	5	29	2	2	M	RD, SAM, MAc, SMA, CS
2012 (127)	India	105	156	35	46	7	9	M	SMA, ST, CS, SAM, ARDS, MOD
2012 (128)	Indonesia	1,541	1,837	400	199	46	18	M	SMA, CS, RD, Jd
2012 (129)	Pakistan	37	39	33	26	1	1	M, P	SMA, CS, ST

[a] M, microscopy; R,rapid diagnostic test; P, PCR; ARDS, acute respiratory distress syndrome; CS, cerebral syndrome (coma or seizures); HD, hepatic dysfunction; Jd, jaundice; MAc, metabolic acidosis; MOD, multiple organ dysfunction; RD, renal dysfunction; SAM, shock or algid malaria; SMA, severe malarial anemia; SpM, splenomegaly; ST, severe thrombocytopenia; NR, not reported.

TABLE 7 Summary of prospective hospital-based studies of severe malaria[a]

Yr of publication (reference)	Location	No. of admissions		No. of severe cases		No. of fatal cases		Diagnostics	Dominant *P. vivax* syndromes
		P. falciparum	*P. vivax*	*P. falciparum*	*P. vivax*	*P. falciparum*	*P. vivax*		
2008 (130)	Indonesia	7,817	2,937	1,570	675	167	46	M, R	SMA, PD, SAM
2010 (131)	India	185	103	79	65	6	4	M, R, P	SMA, ST, MOD
2010 (132)	Brazil	16	90	0	19	0	6	M, P	SMA, ARDS, Jd, RF, MOD
2012 (133)	Sudan	298 (total for both species)		61	18	NR	0	M	SMA, ST, CS, SAM
2012 (134)	India	3	35	3	24	1	0	M	SMA, ST, CS
2012 (135)	Papua New Guinea	3,019 (total for both species)		262	27	1	1	M, R, P	CS, SMA, MAc

[a] NR, not reported/no data; M, microscopy; R, rapid diagnostic test; P, PCR; ARDS, acute respiratory distress syndrome; CS, cerebral syndrome (coma or seizures); Jd, jaundice; MAc, metabolic acidosis; MOD, multiple organ dysfunction; RF, renal failure; SAM, shock or algid malaria; SMA, severe malarial anemia; ST, severe thrombocytopenia.

3,791 admissions with diagnoses of *P. falciparum* and *P. vivax* infections, respectively, with 827 (14%) and 375 (9.9%) being classified as having severe illness (odds ratio [OR] = 1.45; 95% CI = 1.3 to 1.7). The frequencies of death in the patients classified as having severe disease were 17% and 11% with diagnoses of falciparum and vivax malaria, respectively (OR = 1.7; 95% CI = 1.2 to 2.7). These crude estimates of risk cannot be considered definitive, because the methods of classification and diagnostic certainty varied among study centers. The estimates nonetheless suggest that the burdens of severe morbidity and mortality associated with diagnoses of the two species seem only slightly weighted toward falciparum malaria.

Severe malarial anemia, severe thrombocytopenia, pulmonary distress, cerebral syndromes (ranging from seizures to coma), and hepatic and renal dysfunction dominated reported syndromes in patients with a diagnosis of *P. vivax* infection and classified as having severe disease. In general, severely ill patients with a diagnosis of *P. falciparum* infection came with the same syndromes but were more likely to present two or more of these.

Prospective Hospital-Based Studies

Table 7 details findings from prospective hospital-based studies (130–135). The authors of these reports set out to systematically classify patients upon admission to hospital with a primary diagnosis of malaria and to longitudinally collect substantial numbers of patients. Although each of these studies applied distinct classification algorithms for severe illness, the WHO criteria for *P. falciparum* dominated most of them. The studies from Sudan and Papua New Guinea did not provide species-specific hospitalization denominators, and the risk of severe illness at admission is not known. The study in Brazil and the second study from India worked with relatively small numbers, although the Brazilian study came with thorough supporting laboratory studies and definitive diagnostics. That hospital showed that 21% of patients admitted with a diagnosis of *P. vivax* infection had severe disease, and 32% of those did not survive.

More compelling patient numbers came from the studies in Indonesia and India. The Indonesian study showed rates of severe illness with diagnoses of *P. falciparum* and *P. vivax* infections of 20.1% and 23.0%, respectively (OR = 0.84; 95% CI = 0.76 to 0.93). Risks of a fatal outcome with these diagnoses were 10.6% and 6.8%, respectively (OR = 1.63; 95% CI = 1.12 to 2.29). The smaller patient numbers from India showed higher risks of severe illness for both species: 43% and 63% for diagnoses of *P. falciparum* and *P. vivax* infections, respectively (OR = 0.44; 95% CI = 0.27 to 0.72). Risks of death with these diagnoses and classification as severe illness were 7.6% and 6.2%, respectively (OR = 1.25; 95% CI = 0.34 to 4.65). Only two deaths occurred in the large study from Papua New Guinea, one each for falciparum and vivax malaria, and thus did not permit estimation of the risk of death. That study reported particularly rigorous diagnostics and disease classification algorithms.

Prospective Village-Based Studies

Patients reporting to hospital and diagnosed with malaria may not reflect what occurs in villages in areas of endemicity, whose residents often lack access to hospitals where the kinds of studies summarized here may occur. Therefore, studies that examine morbidity in the village setting offer broader insights into the larger burdens of severe morbidity and accompanying elevated risk of mortality. The large longitudinal village-based study reported by Genton and colleagues (136) is thus extremely useful in this regard. The investigators prospectively collected laboratory and clinical data from 73,620 visits to health centers by residents of a rural area of Papua New Guinea (Wosera) from 1997 to 2004. Among these, 9,537 had blood film-confirmed malaria diagnosed as monoinfections by *P. falciparum* (6,886 [72%]) or *P. vivax* (1,946 [20%]), in addition to *P. malariae*, *P. ovale*, and mixed infections (not considered here). Among these clinical visits, 5,584 and 1,613, respectively, had clinical records permitting classification of disease status by the standard algorithm described and applied by the authors. Severe malaria occurred among 342 (6.1%) and 100 (6.2%) patients with diagnoses of *P. falciparum* and *P. vivax* infections, respectively (OR = 0.99; 95% CI = 0.78 to 1.24). This study suggests that the risk of serious and potentially threatening clinical conditions associated with a diagnosis of *P. vivax* infection among residents of rural zones of endemicity may be essentially similar to that for *P. falciparum* infection.

Mothers and Infants

Many of the studies summarized here included mothers, newborns, and young infants in the general hospital populations being evaluated. Two studies from one research group (137, 138), however, carefully separated these vulnerable populations for evaluation of susceptibility to falciparum and vivax malaria. The first study, from Poespoprodjo and colleagues (137), prospectively evaluated 2,570 women at delivery, and 432 had slide-proven malaria: 250 with *P. falciparum*, 146 with *P. vivax*, and 36 with both

species. Parasitemia at birth was significantly associated with preterm birth and stillbirth, but not after controlling for fever and severe anemia. In other words, symptoms of infection rather than infection *per se* seemed to drive the risk of poor outcomes with birth. Women with falciparum malaria had higher risks of both fever (42% versus 24%) and severe anemia (OR = 2.8 versus not significant) than women with vivax malaria.

The second study, led by the same investigator (138), also prospectively evaluated 4,967 infants admitted to hospital, and 1,560 of them were diagnosed with malaria. Case fatality associated with a diagnosis of *P. falciparum* infection was indistinguishable from that associated with a diagnosis of *P. vivax* infection: 13 deaths among 599 infants with *P. falciparum* infection and 6 deaths among 603 infants with *P. vivax* infection ($P = 0.12$). However, infants of <3 months of age and having a diagnosis of *P. vivax* infection were significantly ($P < 0.05$) more likely to have severe anemia (OR = 2.4) and severe thrombocytopenia (OR = 3.3) than very young infants with *P. falciparum*.

McGready and colleagues (139) recently reported a seminal retrospective analysis of pregnancy in 17,613 women exposed or not exposed to acute malaria in the first trimester of pregnancy in western Thailand. They found no differences between diagnoses of *P. falciparum* and *P. vivax* infections in the adjusted odds ratios for miscarriage with asymptomatic malaria (2.7; 95% CI, 2.0 to 3.6) and symptomatic malaria (4.0; 95% CI, 3.1 to 5.1) relative to uninfected women. They concluded that "a single episode of falciparum or vivax malaria in the first trimester of pregnancy can cause miscarriage." These two species equally threatened pregnant women and their fetuses.

SUMMING UP AVAILABLE EVIDENCE

Severe Morbidity and Mortality

Studies over the past decade represent what amount to the first glimpses of patterns of malaria morbidity and mortality in zones of endemicity outside Africa, examined using modern biotechnological tools and sound epidemiological analysis. The evidence derived from these investigations certainly has ambiguities. The uncertainties regarding causation versus association from patient settings have been explained carefully in the context of severe illness and vivax malaria (140, 141). Accepting the necessity of such caution, it is nonetheless striking that this diverse body of evidence points consistently to the same conclusion: a diagnosis of *P. vivax* infection carries similar risks of associated severe illness and death to those for a diagnosis of *P. falciparum* infection. The spectra of syndromes involved are also broadly similar. Although these findings remain preliminary and in need of confirmation by further and more thorough investigations, they nonetheless support abandonment of the "benign" clinical identity that has been attached unequivocally to malaria caused by *P. vivax*. The findings should also give pause in asserting that *P. falciparum* in Africa is the dominant threat to human health posed by malaria globally. The large burdens of *P. vivax* in the Americas and Asia should be acknowledged as a very significant segment of the global malaria problem.

An Error Rooted in History

The assessment of vivax malaria as often severe and threatening to life in many settings where it is endemic, even if only by association at this point, calls for an understanding of how a classification as benign became so firmly entrenched in modern malariology. This review places much weight on the expressed views of Kitchen in Boyd's 1949 text of malariology. The extraordinarily rich technical detail of clinical and parasitological courses in Kitchen's chapters, taken with the large numbers of patients evaluated, certainly appears thorough and authoritative. No body of work before or since equals this scope and depth. In retrospect, however, the work may be seen as having failed to reconcile the seemingly benign parasitological course with demonstrably severe states of illness, as well as compelling evidence of fatal outcomes. As the history of malariology played out over the 6 decades since publication of the Boyd textbook, however, the authoritative and definitive assignment of benign identity to vivax malaria stood unchallenged.

The malariologists of the era that followed that publication oversaw the Global Malaria Eradication Campaign and the elimination of endemic malaria from their homelands in North America and Europe. Paul Russell's 1955 book *Man's Mastery of Malaria* (142) seemed to herald the end of malariology in medicine and public health. Russell remarked in the preface to that book that "one can nevertheless be confident that malaria is well on its way toward oblivion." The global nadir of endemic malaria indeed occurred in the early to mid-1960s, but "oblivion" was not what followed for these diseases. The global eradication program was abandoned as untenable in 1969, and malaria resurged powerfully in the 1970s (143).

By the 1980s, it became clear that real action in malariology was again required. The malariologists of that era naturally looked to the relatively extensive first-hand experience of the earlier malariologists, particularly because the vast majority of the new malariologists lived and worked where endemic malaria no longer occurred. With this perspective, one may grasp the tremendous influence of Boyd's thorough two-volume set, containing rich chapters authored by the malariologists who worked through the eventful and malarious first half of the 20th century. Thus, Kitchen's chapters on clinical malaria—widely accepted then and now as authoritative and definitive—may fairly be considered among the primary sources of "benign" vivax malaria as a tenet of contemporary malariology.

A hiatus from research on vivax malaria began in the 1950s and effectively continues today. This arrest of progress was multifactorial and was influenced by (i) the near abandonment of malariology during the 1960s; (ii) the rejuvenation of malariology by the resurgence of the disease; (iii) the ability to unleash the tools of the biotechnological revolution upon *P. falciparum* in continuous culture in laboratories, beginning during the late 1970s, versus the inability to do so with *P. vivax* until the present; (iv) the narrow focus on the unrelenting African malaria problem dominated by *P. falciparum*; and (v) the effectively untested and unchallenged hypothesis of benign consequences of vivax malaria. Each of these factors played in the eclipse of vivax malaria in research by the pervasive supposition of a global malaria mortality problem heavily weighted upon a single continent by a single species. The graphs in Fig. 3 illustrate this history—the decline of malariology during the 1950s and 1960s and the emergent primacy of falciparum malaria during the rejuvenation of malariology, contrasted with the chronic neglect of vivax malaria.

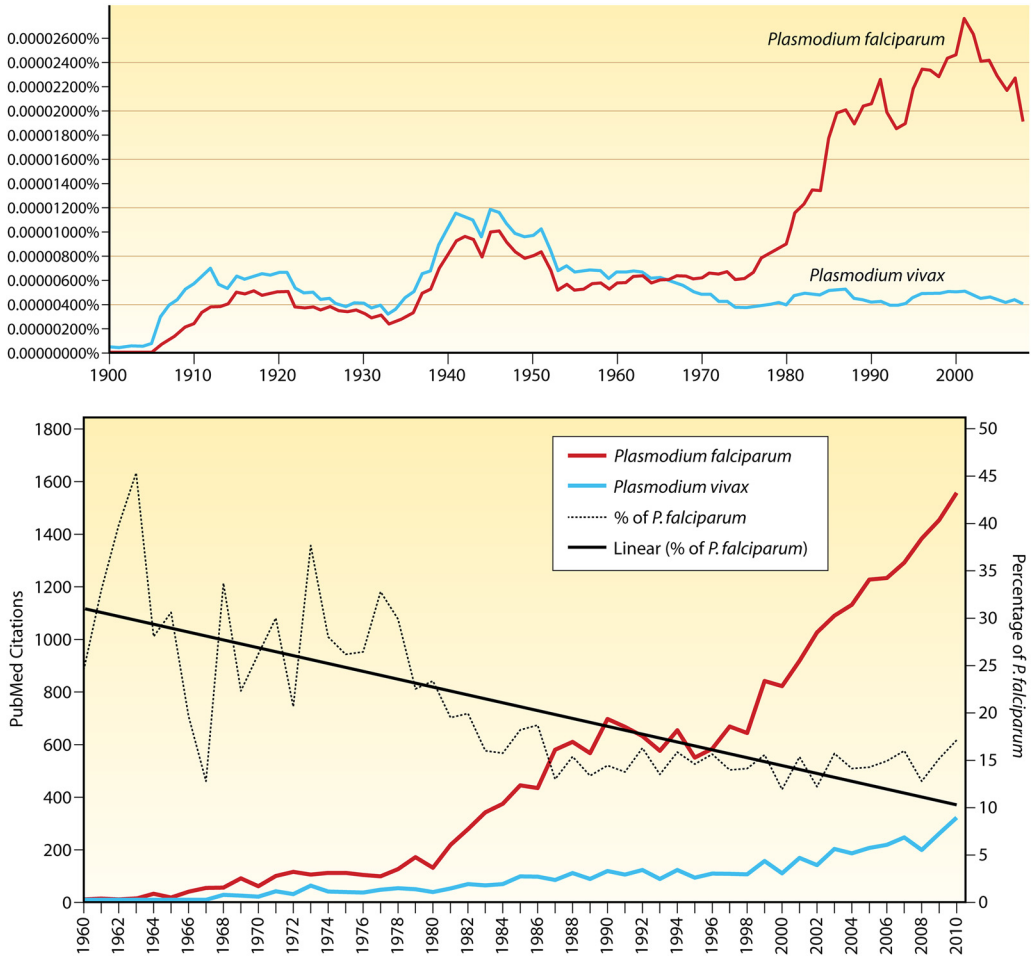

FIG 3 (Top) Graph illustrating citations in books for *Plasmodium falciparum* and *Plasmodium vivax* from 1900 to 2008, generated by use of the tool at http://books.google.com/ngrams. (Bottom) Citation data from PubMed since 1960. (Reproduced from reference174, which was published under a Creative Commons license.)

Benign Vivax Malaria Fallacy

This review considers the weaknesses inherent in the hypothesis of benign consequences of malaria caused by *P. vivax*. The presumption of harmlessness of this species originally derived from the pre-Laveran clinical classification schemes. Benign and malignant malarias, in a clinical sense, certainly existed and still do, but we now recognize these distinctions among all of the human plasmodial organisms. No species is either uniformly dangerous or harmless, and there is little understanding of what drives the distinctions. In the instance of *P. vivax*, the consistency of relatively low and apparently self-limiting parasitemias reinforced the presumption of a typically, if not uniformly, harmless course. Kitchen's keen observation on the analytical approaches taken by the immediate post-Laveran malariologists who preceded him suggested a need to have species identity conform to the established clinical classifications. He understood this as scientifically flawed, but the behavior of the parasite in peripheral blood in his carefully controlled experiments appears to have misled him to affirm a clinical identity for *P. vivax*, i.e., "benign."

Recent studies reported from settings where malaria is endemic prompted examination of the evidence underpinning the benign identity of *P. vivax*. The effectively buried mortality data on malaria therapy for neurosyphilis align well with the contemporary evidence, i.e., a 5% to 15% risk of death with severe illness, with death being caused by severe anemia, respiratory distress, renal failure, and other syndromes. Vivax malaria is not benign but is often pernicious, even with relatively very low burdens of parasites in peripheral blood. The data illustrated in Fig. 4 provide an example of such. The contrast with relative parasitemia levels in patients admitted to the same hospital and diagnosed with *P. falciparum* infection is striking and offers a potentially very useful analytical control—unless comorbidities occurred far more frequently in patients diagnosed with *P. vivax* infection than in those with *P. falciparum* infection, these observations point to the operation of distinct mechanisms of pathogenesis (see below) regarding parasite burdens in peripheral blood.

The available evidence, both old and new, supports an acknowledgment of the fallacy of benign identity for most strains of *P. vivax*. Vivax malaria comes with the risk of life-threatening illness as often as falciparum malaria in many populations exposed to both infections. Regardless of the degree of association versus causality in mortality, *P. vivax* should be recognized as pernicious. This implies no diagnostic or taxonomic meaning or merit, nor does it infer a quantitative risk of a pernicious course. The identity

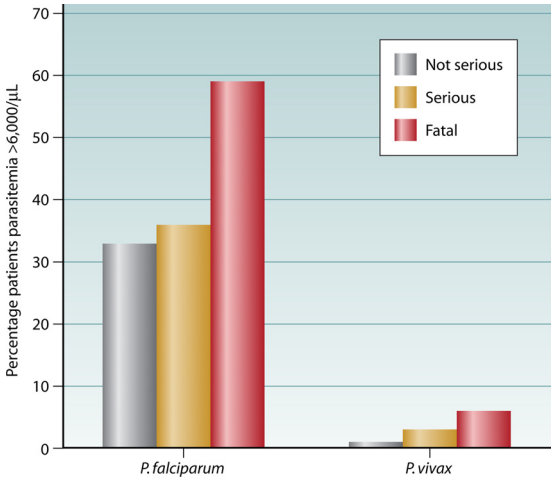

FIG 4 Proportions of patients with not serious, serious, or fatal disease with a diagnosis of *P. falciparum* or *P. vivax* infection and having parasitemias of >6,000/μl among patients hospitalized with a primary diagnosis of malaria at a hospital in Sumba, Indonesia. (Reproduced from reference 128 with permission.)

simply indicates an inherent ability to provoke threatening clinical conditions under as yet undefined circumstances. In contrast, the benign identity long linked to this species inferred an inherent inability to do so, as explicitly stated by Kitchen. This view, no longer withstanding available evidence, largely explains the now unsupportable deep neglect of this infection and its many consequences accumulated over 6 decades of arrested scientific progress.

IMPLICATIONS

Vivax Malaria Threatens Life

The evidence summarized in this review effectively dismisses the notion that vivax malaria rarely threatens life. The most recent evidence, obtained from varied zones of endemicity, by various methods, and by various investigators, consistently shows that a diagnosis of vivax malaria is very often associated with at least potentially life-threatening conditions, apparently about as often as with a diagnosis of *P. falciparum* infection. How *P. vivax* does this is a very important question, but the lack of understanding of pathogenesis should not diminish the importance of the core implication found in the sum of these many findings: *P. vivax* regularly kills people, and probably in very substantial numbers. Whether that occurs directly or indirectly as a consequence of underlying vulnerabilities in the host is, for now, academic relative to the consequences. The burdens of severe disease and death approximate those imposed by falciparum malaria. Effective diagnosis and treatment of the infection would, as it does for falciparum malaria, greatly mitigate the risk of death somehow associated with the diagnosis. The perception of vivax malaria as benign, however, has thwarted development of effective prevention, control, diagnosis, and treatment tools for this infection—the current frontline therapies for vivax malaria, chloroquine and primaquine, have been in continuous use since 1952. This treatment was never suitable for malaria as it occurs in settings of endemicity due to concerns of toxicity, and its efficacy has been known to be eroding for over 2 decades.

Coping with the Threat

Humanity has approached the problem of vivax malaria with what the evidence summarized here suggests is a profound misunderstanding and grievous underestimation of the harm caused. Appreciation of *P. vivax* as a killer should spark a reconsideration of priorities in how we address the global burden of malaria, which have been focused heavily on *P. falciparum* with respect to science and on Africa with respect to mobilizing resources against these diseases. Risk among the billions living in areas of endemicity in Asia and the Americas should be considered a major problem involving both species as essentially equal agents of severe morbidity and mortality. Focusing therapy and other interventions solely on falciparum malaria, with exclusion of a strategy to address the impact upon vivax malaria, is irrational and irresponsible. Some nations in Asia where malaria is endemic, for example, have deployed rapid diagnostic tests capable of detecting only *P. falciparum*. Furthermore, control measures limited to mosquito nets and diagnosis and treatment of the acute attack, even with successful diagnosis of vivax malaria, have a relatively limited impact on endemic vivax malaria (144, 145). The appropriately aggressive and costly measures aimed at containing the emergence of artemisinin-resistant *P. falciparum* in the Mekong region of Southeast Asia have scarcely affected vivax malaria. The intransigence of reemergent *P. vivax* in the Republic of Korea, a financially and technically endowed nation, further highlights the difficulty of dealing with this complex parasite by use of available tools (146).

The imperviousness of the dormant hypnozoite of *P. vivax* to such measures likely explains these observations. Controlling and eliminating vivax malaria will require systematic attack of the hypnozoite reservoir by the national programs responsible for malaria diagnosis and treatment. This singularly difficult task, thanks to the gross inadequacy of the only drug available, primaquine, has been programmatically and scientifically neglected under the false aegis of benign consequence. Mobilizing national malaria control programs to take on the hypnozoite will first require mobilizing the science community to develop solutions to the 60-year-old primaquine toxicity problem (147, 148).

FUTURE PERSPECTIVES

Malariology of the past 50 years has been dominated by the research and development imperatives of drugs and vaccines aimed principally at *P. falciparum*. Laboratories in developed North America and Europe, where malaria is nonendemic, have driven that agenda (149). The taming of the blood stages of *P. falciparum* to continuous culture in those laboratories in the 1970s (150) spawned tremendous advances in understanding the cellular and molecular biology of this dangerous parasite, including the development of powerful new and essential chemotherapeutic tools. In contrast, *P. vivax* has not been thus tamed and imposes difficult obstacles to research agendas in relatively sophisticated laboratories lacking access to patients with vivax malaria. The long neglect of *P. vivax* due to ignorance of its public health importance, and the attendant lack of scientific progress, should be actively redressed. Research and development focused on this parasite are urgently needed to cope with the real threat it poses to human life. The following highlights areas of particular promise and priority.

Clinical Epidemiology

The authors of the studies of malaria morbidity and mortality in zones of endemicity reviewed here followed their training, instincts, and perspective in designing their investigations. As with any such clinical investigation, ambiguities haunt the findings to greater or lesser degrees and in specific areas, depending upon approach. This is true across the spectrum of studies. Effort was taken in review to highlight weaknesses and accompanying uncertainty in order to guide judgments of analytical worthiness, but also to foster more robust investigations in the future. The sum of available evidence, compelling as it appears, could be made a great deal stronger by systematic approaches to patient recruitment, case definition and ascertainment, diagnostics, and coinfection and underlying disease assessments. The development of an expert consensus on standards for case reporting, retrospective and prospective hospital-based studies, and, importantly, village-based assessments of morbidity and mortality by species should be undertaken. The availability of such standards, as well as substantial investments in carrying out these investigations across representative zones of endemicity, may ultimately shed light upon real rather than imagined global burdens of morbidity and mortality imposed by these parasites. The peril in not developing and following evidence is perhaps made clear in the case of the global *P. vivax* problem: expression of that danger may be found in the obsolete and ineffective scientific and clinical tools at our disposal to understand and combat this threat.

Chemotherapeutics

The conspicuously poor state of chemotherapeutics for vivax malaria has been discussed and detailed here and elsewhere (147–149). The aim of the following is to emphasize the consequences of that state of affairs in order to help crystallize a strategy for coping with the threats imposed.

Prevalent G6PDd in zones of endemicity, along with the certain risk of primaquine causing serious harm, effectively disables that otherwise critical tool of treatment. A replacement drug, tafenoquine, has been in clinical development since the 1980s and is not yet licensed. Although that drug also causes hemolysis in G6PDd patients, a formulation that minimizes that risk is being decisively considered in its further development. Recognizing and accepting the fact of mortal threat with acute vivax malaria requires such deliberate action to revive access to safe and effective therapy as an urgent priority for the community of science.

Failure to attack the hypnozoite reservoir in patients causes a single infectious bite by a mosquito to result in repeated attacks and opportunities for further transmission. Such repeated insults, each carrying possible delays in diagnosis and the risk of ineffective treatment, may be instrumental in the morbidity and mortality figures reviewed here. Indeed, the approximate rates of death among the severely ill diagnosed with *P. vivax*, about 5 to 15% in the many studies reviewed here, approximate those that occurred in neurosyphilis patients, where deliberate repeated attacks and delayed and inadequate therapy occurred. It is at least possible that in settings where malaria is endemic, inadequate therapy and repeated relapses are the primary instruments of severe morbidity and mortality with vivax malaria. Taming the toxicity of primaquine to G6PDd patients by any means, or developing a safer drug, should be considered the highest priority for research and development in malaria. An effective vaccine would be ideal, but those against *P. vivax* lag very far behind efforts for such against *P. falciparum*, and even these have yet to offer real promise for a tool relevant to declared elimination goals (excepting the untried transmission-blocking vaccines, which still have great promise). For the time being, drugs should be emphasized, especially given the almost wholly unexplored potential of these tools against the many parasite species, stages, and clinical states known collectively as the endemic malarias.

A Plausible and Testable Hypothesis on Pathogenesis

Kitchen's mute dismissal of mortality in neurosyphilis patients left no plausible and testable hypothesis to reconcile a benign identity for *P. vivax* with those lethal outcomes. Hypotheses that attempt to explain natural phenomena must be reconciled to seemingly conflicting but valid observations—the conflict should be explained rationally by a hypothesis that is compatible with available evidence, and thus plausible. With regard to the apparent conflict between relatively very low parasite burdens in peripheral blood and the severity of illness in vivax malaria, a plausible and testable hypothesis offering a possible resolution of that conflict is posited below.

Figure 4 illustrates the primary conundrum with serious illness in vivax malaria–relatively very-low-grade parasitemias seem to provoke grave clinical conditions. If one rejects underlying diseases dominating patients with vivax but not falciparum malaria as the likely explanation for these contrasting sets of data, an accounting grounded in species-specific pathogenesis is required. The relatively greater immunogenic capacity of *P. vivax* than that of *P. falciparum* seems inadequate as the sole basis of such profound distinctions in parasite burdens in blood across those grades of illness. Other factors must lend to a credible accounting linked to pathogenesis.

The quantitative relationship between *P. falciparum* biomass and the risk of severe disease or likely modulators is established in epidemiology (151, 152), the clinic (153, 154), and the laboratory (155, 156). No lone mechanism drives poor outcomes in that relationship, however. Acute malaria causes at least several clinically distinct threatening dysfunctions in the African setting (157), and others in more diverse settings (158). This diversity compounds the difficulty of assessing precise cellular and molecular mechanisms of pathogenesis. Kirchgatter and del Portillo (159) explain this complexity in *P. falciparum* and cite the 3 parasite phenotypes likely to mediate virulence in that infection: cyto-adherence, rosetting, and antigenic variation. Although apparently important differences between *P. falciparum* and *P. vivax* occur among these phenotypes (160, 161), none gets to the heart of the primary question—how do such low-grade parasitemias cause such severe disease states in vivax malaria? The quantitative threat of parasite biomass, regardless of precise phenotypes at work within it, is the primary problem to reconcile in severe vivax malaria.

One possible means of explaining the apparent disobedience of the overarching biomass-severity rule by *P. vivax* is consideration of the sole practical means of quantifying that biomass—examination of the peripheral blood. It is well known that *P. falciparum* causes the membranes of the red blood cells it infects to become relatively rigid. In the absence of lesions in the circulation, this effectively impounds the parasites within the sinuses of that organ (162). Although important exceptions likely occur, in general, parasite counts in blood likely correlate well with total biomass. The well-developed cyto-adhesive molecular machinery in this

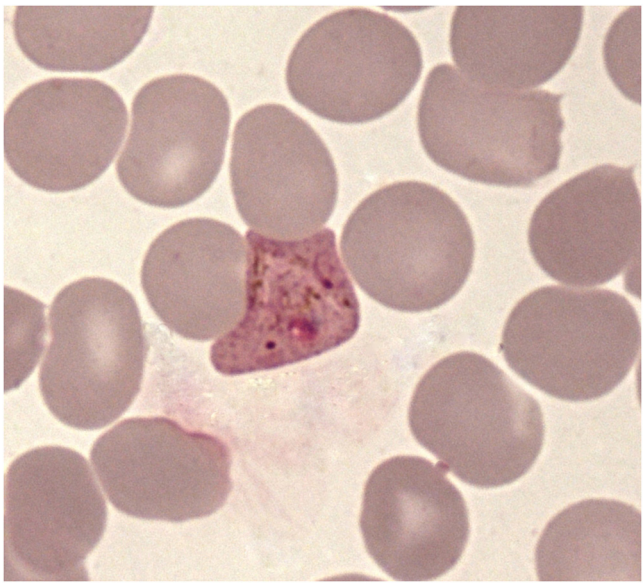

FIG 5 Mature trophozoite of *P. vivax* in a Giemsa-stained thin blood film under oil-immersion magnification. (Photomicrograph by Lenny Ekawati, Jakarta, Indonesia.)

infection likely represents adaptations against certain destruction in the otherwise inevitable passage through the spleen (160)—adhesion to vascular endothelium may be the sole refuge available to this sinus-bound species. *Plasmodium vivax*, in contrast, possesses relatively poor adhesive machinery (161) and typically enlarges the red blood cells it infects. These features would seem to render the parasites vulnerable to effective removal in the spleen, as well as offer a more consistent correlation of parasitemia to absolute biomass. However, this parasite exerts a profoundly different effect upon the red blood cells it inhabits—they become more flexible than uninfected red blood cells (albeit more fragile) (163, 164). That key finding, supported by the conspicuous mutability of infected RBC familiar to experienced microscopists observing these forms in stained blood films (Fig. 5), suggests that *P. vivax*-infected red blood cells may be able to access tissues beyond the vascular sinuses.

The specific epitaph for this species, "vivax," is Latin for "vivacious"—a reference to the conspicuously active amoeboid movement of mature asexual trophozoites observed in living specimens in peripheral blood wet mount examinations. Such behavior, seemingly pointless in a passive floater confined to blood circulation (living *P. falciparum* trophozoites in RBC exhibit no such motility), may be essential in accessing and navigating tissues beyond the blood circulation. The trophozoites may be thought of as motile amoebae cloaked in flexible reticulocyte membranes, perhaps actively navigating the extravascular habitats of the erythroid cells.

Uninfected reticulocytes maturing in marrow sinuses naturally penetrate endothelial cells of the marrow vasculature by "boring" 2.5-μm pores at the parajunctional (thinnest) zone of those cells (165). This ability does not occur in younger erythroid cells and vanishes when the reticulocytes mature to erythrocytes, thus regulating the composition of the erythroid population in blood. Reticulocytes infected by *P. vivax* trophozoites successfully traversed experimental microfluidic chambers with a 2-μm diameter (164). If infected reticulocytes retain the ability to penetrate vascular endothelium, such a capability may offer access to the extravascular tissues of marrow rich in immature blood cells—merozoites of *P. vivax* are obligately preferential in invading these cells. Likewise, reticulocytes infected within the marrow may access vascular sinuses. Such a range of habitat perhaps spares *P. vivax* the requirement for vascular endothelial cyto-adhesion (in *P. falciparum* fashion) as a necessary means of survival. The otherwise inexplicable self-limiting fastidiousness of invasive merozoites of *P. vivax* toward reticulocytes perhaps represents a key strategy for avoiding impoundment within vascular sinuses.

Most of the behavioral, physical, cellular, and molecular attributes of this species seem ideally suited to living in hemopoietic tissues rather than exclusively or even predominantly in the vascular sinuses. Viable asexual trophozoites of *P. vivax* in infected reticulocytes (or erythroblasts) have indeed been observed in the bone marrow (95, 166–171) and spleen (172). In one case, a subpatent parasitemia confirmed by PCR contrasted with a ruptured spleen very heavily laden with *P. vivax*-infected reticulocytes (175). Rupture or infarct of the spleen is a relatively rare and seriously threatening complication of vivax malaria (173), and this seems to reflect a natural affinity for hemopoietic tissues by *P. vivax* parasites.

These observations beg an obvious question: what proportion of *P. vivax* biomass in any given host occurs in blood circulation versus other tissues? If the answer to the question reveals a relatively small proportion, it may offer a plausible explanation for the contrasting graphs in Fig. 4 and, ultimately, the illusion of *P. vivax* as a benign infection. Vivax malaria may be primarily an infection of hemopoietic tissues rather than vascular sinuses—this is the plausible and testable hypothesis posited here. In one patient with blood and bone marrow examined by quantitative PCR, only the marrow showed positivity for *P. vivax* (168). Assessment of both compartments in this manner offers a relatively simple and decisive means of testing this hypothesis. Such work is now being actively pursued in laboratories in Indonesia.

Implications of Extravascular Sinus Infection

Should the hypothesis of *P. vivax* biomass residing primarily exterior to the vascular sinuses be proven true, assumptions in clinical medicine, epidemiology, and public health would require reconsideration in light of this insidious threat. Parasites in peripheral blood, regardless of counts, may represent a small and variable proportion of the total biomass and clinical threat. In surveys of the prevalence of parasitemia in populations in areas of endemicity, those having parasites detectable in peripheral blood perhaps represent a small proportion of the infected individuals.

Clinical management of vivax malaria requires reliable assessments of parasite biomass. The hypothesized bulk of threatening biomass occurring exterior to vascular sinuses may explain the relatively high mortality rate with the Madagascar strain of *P. vivax* compared to *P. falciparum* in neurosyphilis patients (57)—the providers could more closely monitor and control the *P. falciparum* biomass through blood film examination, whereas a biomass of *P. vivax* exterior to vascular sinuses could expand dangerously without detection. Should the hypothesis of hemopoietic infection be proven true, safe monitoring of hospitalized patients with acute vivax malaria may require laboratory examination of bone marrow aspirates, applying some means of objectively quantifying parasite load in that tissue.

If the parasites reside principally in marrow and the spleen, such an observation would also raise important questions regarding measurements of the burden of infection in any given population in an area of endemicity. Estimates of the global population at risk and of endemicity (2, 5) hinge upon the prevalence of parasites in peripheral blood film examinations. Parasites concealed within the marrow and spleen, and certainly hypnozoites in the liver, may all represent substantially larger proportions of the populations surveyed. The true prevalence of *P. vivax* in zones of endemicity may be considerably higher than that suggested by mass blood film examinations.

Conclusions

Vivax malaria is a threatening infection despite relatively low-grade parasitemias in peripheral blood. This should have been acknowledged and understood from the long experience with neurosyphilis therapy, which began nearly a century ago and persisted into the 1950s. The presumption of death as a rare outcome, rooted in antiquated and flawed clinical classifications, hinged upon the finding of consistently low parasitemias. The hypothesis, derived from closely observed induced infections, disregarded critical clinical facts: the routine mortality in neurosyphilis therapy and broader patient populations in areas of endemicity and the physiological threat inherent in repeated severe paroxysms. The very-well-documented course of this infection, with the exception of parasitemia, carries all of the attributes of perniciousness historically linked to falciparum malaria, including severe disease and fatal outcomes. A systematic analysis of the parasite biomass in severely ill patients that includes measurements in the blood, marrow, and spleen may offer an explanation for this historic misunderstanding. However, regardless of how this parasite is pernicious, recent data demonstrate that the infection comes with a significant burden of morbidity and associated mortality. The extraordinary burden of malaria is not heavily weighted upon any single continent by a single species of parasite—it is a complex problem for the entire world of endemicity, and both species are of fundamental importance. Humanity must rally substantial resources, intellect, and energy to counter this daunting but profound threat.

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REFERENCES

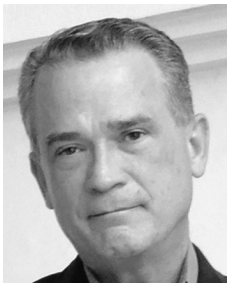
1. **Mendis K, Sina BJ, Marchesini P, Carter R.** 2001. The neglected burden of *Plasmodium vivax* malaria. Am. J. Trop. Med. Hyg. **64**:97–106.
2. **Guerra CA, Howes RE, Patil AP, Gething PW, Van Boeckel TP, Temperley WH, Kabaria CW, Tatem AJ, Manh BH, Elyazar IR, Baird JK, Snow RW, Hay SI.** 2010. The international limits and population at risk of *Plasmodium vivax* transmission in 2009. PLoS Negl. Trop. Dis. **4**:e774. doi:10.1371/journal.pntd.0000774.
3. **Guerra CA, Snow RW, Hay SI.** 2006. Mapping the global extent of malaria in 2005. Trends Parasitol. **22**:353–358.
4. **Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI.** 2005. The global distribution of clinical episodes of *Plasmodium falciparum.* Nature **434**: 214–217.
5. **Gething PW, Elyazar IRF, Moyes CL, Smith DL, Battle KE, Guerra CA, Patil AP, Tatem AJ, Howes RE, Myers MF, George DB, Horby P, Wertheim HFL, Price RN, Müeller I, Baird JK, Hay SI.** 2012. A long neglected world malaria map: *Plasmodium vivax* endemicity in 2010. PLoS Negl. Trop. Dis. **6**:e1814. doi:10.1371/journal.pntd.0001814.
6. **Miller LH, Mason SJ, Clyde DF, McGinniss MH.** 1976. The resistance factor to *Plasmodium vivax* in blacks. The Duffy-blood-group genotype, FyFy. N. Engl. J. Med. **295**:302–304.
7. **Howes RE, Patil AP, Piel FB, Nyangiri OA, Kabaria CW, Gething PW, Zimmerman PA, Barnadas C, Beall CM, Gebremedhin A, Menard D, Williams TN, Weatherall DJ, Hay SI.** 2011. The global distribution of the Duffy blood group. Nat. Commun. **2**:266.
8. **Hay SI, Okiro EA, Gething PW, Patil AP, Tatem AJ, Guerra CA, Snow RW.** 2010. Estimating the global clinical burden of *Plasmodium falciparum* malaria in 2007. PLoS Med. **7**:e1000290. doi:10.1371/journal.pmed.1000290.
9. **Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW.** 2004. The global distribution and population at risk of malaria: past, present and future. Lancet **4**:327–336.
10. **World Health Organization.** 2010. World malaria report 2010. World Health Organization, Geneva, Switzerland.
11. **Project UNM, Working Group on Malaria.** 2005. Coming to grips with malaria in the new millenium. Task force on HIV/AIDS, malaria, TB and access to essential medicines. Earthscan, London, United Kingdom.
12. **Breman JG, Alilio MS, Mills A.** 2004. Conquering the intolerable burden of malaria: what's new, what's needed: a summary. Am. J. Trop. Med. Hyg. **71**(Suppl 2):1–15.
13. **Finkel M.** 2007. Bedlam in the blood: malaria. Natl. Geogr. July 2007: 31–67.
14. **PATH.** 2011. Staying the course? Malaria research and development in a time of economic uncertainty. PATH, Seattle, WA.
15. **Snow RW, Okiro EA, Gething PW, Atun R, Hay SI.** 2010. Equity and adequacy of international donor assistance for global malaria control: an analysis of populations at risk and external funding commitments. Lancet **376**:1409–1416.
16. **Piggott DM, Atun R, Moyes CL, Hay SI, Gething PW.** 2012. Funding for malaria control 2006–2010: a comprehensive global assessment. Malar. J. **11**:246.
17. **Cappellini MD, Fiorelli G.** 2008. Glucose-6-phosphate dehydrogenase deficiency. Lancet **371**:64–74.
18. **Howes RE, Piel FB, Patil AP, Nyangiri OA, Gething PW, Dewi M, Hogg MM, Battle KE, Padilla CD, Baird JK, Hay SI.** 2012. G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map. PLoS Med. **9**:e1001339. doi:10.1371/journal.pmed.1001339.
19. **Abeyaratne KP, Halpe NL.** 1968. Sensitivity to primaquine in Ceylonese children due to deficiency of erythrocytic glucose-6-phosphate dehydrogenase. Ceylon Med. J. **27**:134–138.
20. **Burgoine KL, Bancone G, Nosten F.** 2010. The reality of using primaquine. Malar. J. **9**:376.
21. **Baird JK, Hoffman SL.** 2004. Primaquine therapy for malaria. Clin. Infect. Dis. **39**:1336–1345.

22. **Goller JL, Jolley D, Ringwald P, Biggs BA.** 2007. Regional differences in the response of *Plasmodium vivax* malaria to primaquine as anti-relapse therapy. Am. J. Trop. Med. Hyg. **76**:203–207.
23. **Galappaththy GN, Omari AA, Tharyan P.** 2007. Primaquine for preventing relapses in people with *Plasmodium vivax* malaria. Cochrane Database Syst. Rev. **2007**:CD004389.
24. **Kitchen SF.** 1949. Chapters 40–43, p 966–1045. *In* Boyd MF (ed), Malariology: a comprehensive survey of all aspects of this group of diseases from a global standpoint, vol. II. W B Saunders Company, Philadelphia, PA.
25. **Dhingra N, Jah P, Sharma VP, Cohen AA, Jotkar RM, Rodriguez PS, Bassani DG, Suraweera W, Laxminaryan R, Peto R.** 2010. Adult and child mortality in India. Lancet **376**:1768–1774.
26. **World Health Organization.** 2008. World malaria report 2008, p 1–190. WHO/HTM/GMP/20081. World Health Organization, Geneva, Switzerland.
27. **Hay SI, Gething PW, Snow RW.** 2010. India's invisible malaria burden. Lancet **376**:1716–1717.
28. **Elyazar IRF, Hay SI, Baird JK.** 2011. Malaria distribution, prevalence, drug resistance and control in Indonesia. Adv. Parasitol. **74**:41–175.
29. **Elyazar IRF, Gething PW, Patil AP, Royagah H, Kusriastuti R, Wismarini DM, Tarmizi SN, Baird JK, Hay SI.** 2011. *Plasmodium falciparum* malaria endemicity in Indonesia in 2010. PLoS One **6**:e21315. doi: 10.1371/journal.pone.0021315.
30. **Murray CJ, Rosenfeld LC, Lim SS, Andrews KG, Foreman KJ, Haring D, Fullman N, Naghavi M, Lozano R, Lopez AD.** 2012. Global mortality between 1980 and 2010: a systematic analysis. Lancet **379**:413–431.
31. **Doolan DL, Dobaño C, Baird JK.** 2009. Acquired immunity to malaria. Clin. Microbiol. Rev. **22**:13–36.
32. **Branch O, Casapia WM, Gamboa DV, Hernandez JN, Alava FF, Roncal N, Alvarez E, Perez EJ, Gotuzzo E.** 2005. Clustered local transmission and asymptomatic *Plasmodium falciparum* and *Plasmodium vivax* malaria infections in a recently emerged, hypoendemic Peruvian Amazon community. Malar. J. **4**:27.
33. **Harris I, Sharrock WW, Bain LM, Gray KA, Bobogare A, Boaz L, Lilley K, Krause D, Vallely A, Johnson ML, Gatton ML, Shanks GD, Cheng Q.** 2010. A large proportion of asymptomatic *Plasmodium* infections with low and sub-microscopic parasite densities in the low transmission setting of Temotu Province, Solomon Islands: challenges for malaria diagnostics in an elimination setting. Malar. J. **9**:254.
34. **Sternberg GM.** 1884. Malaria and malarial diseases. William Wood & Company, New York, NY.
35. **Coatney GR, Collins WE, Warren M, Contacos PG.** 1971. The primate malarias. US Government Printing Office, Washington, DC.
36. **Harrison GA.** 1978. Mosquitoes, malaria & man: a history of the hostilities since 1880. E P Dutton, New York, NY.
37. **Ewing J.** 1902. Contribution to the pathological anatomy of malaria fever. J. Exp. Med. **6**:119–180.
38. **Covell G, Russell PF, Swellengrebel NH.** 1953. Malaria terminology: report of a drafting committee appointed by the World Health Organization. WHO series 13. WHO, Geneva, Switzerland.
39. **Wilcox A.** 1960. Manual for the microscopical diagnosis of malaria in man. US Government Printing Office, Washington, DC.
40. **Nicol WD.** 1956. General paralysis of the insane. Br. J. Vener. Dis. **32**:9–16.
41. **Nicol WD.** 1932. General paralysis: report of 579 case treated by malaria in the London County mental hospitals. Br. J. Psychiatry **78**:946.
42. **James SP, Nicol WD, Shute PG.** 1936. Clinical and parasitological observation on induced malaria. Proc. R. Soc. Med. **29**:879–894.
43. **Nicol WD.** 1927. The care and management of induced malaria. J. Mental Sci. **73**:209–217.
44. **Nicol WD.** 1932. A review of 7 year's malaria therapy in general paralysis. J. Mental Sci. **78**:843–866.
45. **Fong TCC.** 1937. A study of the mortality rate and complications following therapeutic malaria. South. Med. J. **30**:1084–1088.
46. **Martin JP.** 1972. Conquest of general paralysis. Br. Med. J. **3**:159–160.
47. **Nicol WD.** 1929. The treatment of general paralysis by malaria. Br. J. Vener. Dis. **5**:85–94.
48. **Kragh JV.** 2010. Malaria therapy for general paralysis of the insane in Denmark. Hist. Psychiatry **21**:471–486.
49. **O'Leary PA, Welsh AL.** 1933. Treatment of neurosyphilis with malaria: observations on nine hundred and eighty-four cases in the last nine years. JAMA **101**:489–501.
50. **Karnosh LJ, Williams GH.** 1935. Some unusual complications in malaria therapy. Ohio State Med. J. **31**:193.
51. **Haskins J.** 1931. Review of 100 malarial treated cases of general paralysis. Psychiatry Q. Albany **5**:193.
52. **Krauss W.** 1932. Analysis of reports of 8,354 cases IMPF-malaria. South. Med. J. **25**:537–541.
53. **Reid B.** 1932. General paralysis: result of eight years of malarial therapy. Br. J. Psychiatry **78**:867–877.
54. **Lilly GA.** 1925. Treatment of general paralysis at Hanwell Mental Hospital Br. J. Psychiatry **71**:267–278.
55. **Rudolf GM.** 1936. Recent advances in therapeutic (induced) malaria. J. Neurol. Psychopathol. **16**:239–255.
56. **Nicol WD.** 1933. The relation of syphilis to mental disorder and the treatment of G.P.I. by malaria. Br. J. Vener. Dis. **9**:219–229.
57. **James SP, Nicol WD, Shute PG.** 1932. A study of induced malignant tertian malaria. Proc. R. Soc. Med. **XX**:1153–1186.
58. **Garnham PC, Bray RS, Bruce-Chwatt LJ, Draper CC, Killick-Kendrick R, Sergiev PG, Tiburskaja NA, Shute PG, Maryon M.** 1975. A strain of *Plasmodium vivax* characterized by prolonged incubation: morphological and biological characteristics. Bull. World Health Organ. **52**:21–32.
59. **Dauer CC, Faust EC.** 1937. Malaria mortality in the United States, with special reference to the southeastern states. South. Med. J. **30**:939–943.
60. **Prokopenko LI.** 1959. On epidemiology of fulminant *P. vivax* malaria, p 80–102. *In* Beklemishev VN, Rashina MG (ed), Transactions of the Moscow Martinovski Institute of Medical Parasitology and Tropical Medicine. Institute of Medical Parasitology and Tropical Medicine, Moscow, Russia. (In Russian.)
61. **Lysenko AY.** 1960. Use of quinocide in treatment and prophylaxis of vivax malaria. Bull. World Health Organ. **22**:641–662.
62. **Swellengrebel NH.** 1950. The malaria epidemic of 1943–1946 in the province of North Holland. Trans. R. Soc. Trop. Med. Hyg. **43**:445–461.
63. **Luxemburger C, Ricci F, Nosten F, Raimond D, Bathet S, White NJ.** 1997. The epidemiology of severe malaria in an area of low transmission in Thailand. Trans. R. Soc. Trop. Med. Hyg. **91**:256–262.
64. **Hyman A.** 1945. Clinical masquerade of malaria. U. S. Navy Med. Bull. **45**:287–303.
65. **Most H, Hayman JM, Jr.** 1946. Uncommon clinical manifestations of vivax malaria. JAMA **130**:480–485.
66. **Romanenko AP.** 1936. Two cases of comatose from tertian malaria. Med. Parazitol. (Mosk.) **5**:925–926. (In Russian.)
67. **Tarajev EM, Gontayeva AA, Rotenburg SS.** 1943. Fulminating type of tertian malaria. Sov. Med. **4**:12–14. (In Russian.)
68. **Karunaweera ND, Grau GE, Gamage P, Carter R, Mendis KN.** 1992. Dynamics of fever and serum levels of tumor necrosis factor are closely associated during clinical paroxysms in *Plasmodium vivax* malaria. Proc. Natl. Acad. Sci. U. S. A. **89**:3200–3203.
69. **Hemmer CJ, Holst FG, Kern P, Chiwakata CB, Dietrich M, Reisinger EC.** 2006. Stronger host response per parasitized erythrocyte in *Plasmodium vivax* or *ovale* than in *Plasmodium falciparum* malaria. Trop. Med. Int. Health **11**:817–823.
70. **Perera MK, Carter R, Goonewardene R, Mendis KN.** 1994. Transient increase in circulating gamma/delta T cells during *Plasmodium vivax* malarial paroxysms. J. Exp. Med. **179**:311–315.
71. **Yeo TW, Lampah DA, Tjitra E, Piera K, Gitawati R, Kenangalem E, Price RN, Anstey NM.** 2010. Greater endothelial activation, Weibel-Palade body release and host inflammatory response to *Plasmodium vivax*, compared with *Plasmodium falciparum*: a prospective study in Papua, Indonesia. J. Infect. Dis. **202**:109–112.
72. **Seoh JY, Khan M, Park SH, Park HK, Shin MH, Ha EH, Lee BE, Yoo K, Han HS, Oh S, Wi JH, Hong CK, Oh CH, Kim YA, Park JW.** 2003. Serum cytokine profiles in patients with *Plasmodium vivax* malaria: a comparison between those who presented with and without hyperpyrexia. Am. J. Trop. Med. Hyg. **68**:102–106.
73. **Valecha N, Bagga A, Chandra J, Sharma D.** 1992. Cerebral symptoms with *P. vivax* malaria. Indian Pediatr. **29**:1176–1178.
74. **Yale SH, Adlakha A, Sebo TJ, Ryu JH.** 1993. Bronchiolitis obliterans organizing pneumonia caused by *Plasmodium vivax* malaria. Chest **104**:1294–1296.
75. **Munteis E, Mellibovsky L, Marquez MA, Minguez S, Vazquez E, Diez A.** 1997. Pulmonary involvement in a case of *Plasmodium vivax* malaria. Chest **111**:834–835.
76. **Torres JR, Perez H, Postigo MM, Silva JR.** 1997. Acute non-cardiogenic lung injury in benign tertian malaria. Lancet **350**:31–32.

77. **Curlin ME, Barat LM, Walsh DK, Granger DL.** 1999. Non-cardiogenic pulmonary edema during vivax malaria. Clin. Infect. Dis. **28**:1166–1167.
78. **Hsieh S, Babl FE.** 1999. Vivax malaria complicated by adult respiratory distress syndrome. Clin. Infect. Dis. **28**:1182–1184.
79. **Tanios MA, Kogelman L, McGovern B, Hassoun PM.** 2001. Acute respiratory distress syndrome complicating *Plasmodium vivax* malaria. Crit. Care Med. **29**:665–667.
80. **Beg MA, Khan R, Baig SM, Gulzar Z, Hussain R, Smego RA, Jr.** 2002. Cerebral involvement in benign tertian malaria. Am. J. Trop. Med. Hyg. **67**:230–232.
81. **Makkar RP, Mukhopadhyay S, Monga A, Gupta AK.** 2002. *Plasmodium vivax* malaria presenting with severe thrombocytopenia. Braz. J. Infect. Dis. **6**:263–265.
82. **Lawn SD, Krishna S, Jarvis JN, Joet T, Macallan DC.** 2003. Case reports: pernicious complications of benign tertian malaria. Trans. R. Soc. Trop. Med. Hyg. **97**:551–553.
83. **Spudick JM, Garcia LS, Graham DM, Haake DA.** 2005. Diagnostic and therapeutic pitfalls associated with primaquine-tolerant *Plasmodium vivax*. J. Clin. Microbiol. **43**:978–981.
84. **Habib AG, Singh KS.** 2004. Respiratory distress in nonimmune adults with imported malaria. Infection **32**:356–359.
85. **Lomar AV, Vidal JE, Lomar FP, Barbas CV, de Matos GJ, Buolos M.** 2005. Acute respiratory distress syndrome due to vivax malaria: case report and literature review. Braz. J. Infect. Dis. **9**:425–430.
86. **Thapa R, Patra V, Kundu R.** 2007. *Plasmodium vivax* cerebral malaria. Indian Pediatr. **44**:433–434.
87. **Ozen M, Gungor S, Atambay M, Daldal N.** 2006. Cerebral malaria owing to *Plasmodium vivax*: case report. Ann. Trop. Paediatr. **26**:141–144.
88. **Illamperuma C, Allen BL.** 2007. Pulmonary edema due to *Plasmodium vivax* malaria in an American missionary. Infection **35**:374–376.
89. **Maguire JD, Fenton ME, Susanti AI, Walker JB.** 2007. *Plasmodium vivax*-associated acute respiratory distress syndrome after extended travel in Afghanistan. Travel Med. Infect. Dis. **5**:301–305.
90. **Song JY, Park CW, Jo YM, Kim JY, Kim JH, Yoon HJ, Kim CH, Lim CS, Cheong HJ, Kim WJ.** 2007. Two cases of *Plasmodium vivax* malaria with the clinical picture resembling toxic shock. Am. J. Trop. Med. Hyg. **77**:609–611.
91. **Kumar S, Melzer M, Dodds P, Watson J, Ord R.** 2007. *P. vivax* malaria complicated by shock and ARDS. Scand. J. Infect. Dis. **39**:255–256.
92. **Price L, Planche T, Rayner C, Krishna S.** 2007. Acute respiratory distress syndrome in *Plasmodium vivax* malaria: case report and review of the literature. Trans. R. Soc. Trop. Med. Hyg. **101**:655–659.
93. **Agarwal R, Nath A, Gupta D.** 2007. Noninvasive ventilation in *Plasmodium vivax* related ALI/ARDS. Intern. Med. **46**:2007–2011.
94. **Sarkar S, Bhattacharya P.** 2008. Cerebral malaria caused by *Plasmodium vivax* in adult subjects. Indian J. Crit. Care Med. **12**:204–205.
95. **Lacerda MV, Hipolito JR, Passos LN.** 2008. Chronic *Plasmodium vivax* infection in a patient with splenomegaly and severe thrombocytopenia. Rev. Soc. Bras. Med. Trop. **41**:522–523.
96. **Kotwal RS, Wenzel RB, Sterling RA, Porter WD, Jordan NN, Petruccelli BP.** 2005. An outbreak of malaria in US Army Rangers returning from Afghanistan. JAMA **293**:212–216.
97. **Rifakis PM, Hernandez O, Fernandez CT, Rodriguez-Morales AJ, Von A, Franco-Paredes C.** 2008. Atypical *Plasmodium vivax* malaria in a traveler: bilateral hydronephrosis, severe thrombocytopenia, and hypotension. J. Travel Med. **15**:119–121.
98. **Tan LK, Yacoub S, Scott S, Bhagani S, Jacobs M.** 2008. Acute lung injury and other serious complications of *Plasmodium vivax* malaria. Lancet Infect. Dis. **8**:449–454.
99. **Thapa R, Biswas B, Mallick D, Sardar S, Modak S.** 2009. Childhood *Plasmodium vivax* malaria with severe thrombocytopenia and bleeding manifestations. J. Pediatr. Hematol. Oncol. **31**:758–759.
100. **Valecha N, Pinto RG, Turner GD, Kumar A, Rodrigues S, Dubhashi NG, Rodrigues E, Banaulikar SS, Singh R, Dash AP, Baird JK.** 2009. Histopathology of fatal respiratory distress caused by *Plasmodium vivax* malaria. Am. J. Trop. Med. Hyg. **81**:758–762.
101. **Kasliwal P, Rao MS, Kujur R.** 2009. *Plasmodium vivax* malaria: an unusual presentation. Indian J. Crit. Care Med. **13**:103–105.
102. **Kochar SK, Mahajan M, Gupta RP, Middha S, Acharya J, Kochar A, Das A, Kochar DK.** 2009. Acute attack of AIP (acute intermittent porphyria) with severe vivax malaria associated with convulsions: a case report. J. Vector Borne Dis. **46**:307–309.
103. **Harish R, Gupta S.** 2009. *Plasmodium vivax* malaria presenting with severe thrombocytopenia, cerebral complications and hydrochepalus. Indian J. Pediatr. **76**:551–552.
104. **Kim SA, Kim ES, Rhee MY, Choi SI, Huh HJ, Chae SL.** 2009. A case of myocarditis associated with *Plasmodium vivax* malaria. J. Travel Med. **16**:138–140.
105. **Sarkar S, Saha K, Das CS.** 2010. Three cases of ARDS: an emerging complication of *Plasmodium vivax* malaria. Lung India **27**:154–157.
106. **Siqueira AM, Alexandre MA, Mourao MP, Santos VS, Nagahashi-Marie SK, Alecrim MG, Lacerda MV.** 2010. Severe rhabdomyolysis caused by *Plasmodium vivax* malaria in the Brazilian Amazon. Am. J. Trop. Med. Hyg. **83**:271–273.
107. **Bhatia V, Bhatia J.** 2010. Severe thrombocytopenia with bleeding manifestations in two children secondary to *Plasmodium vivax*. Platelets **21**: 307–309.
108. **Zaki SA, Shanbag P.** 2011. Acute glomerulonephritis: an unusual manifestation of *Plasmodium vivax* malaria. Ann. Trop. Paediatr. **31**:181–184.
109. **Kute VB, Vanikar AV, Ghuge PP, Goswami JG, Patel MP, Patel HV, Gumber MR, Shah PR, Trivedi HL.** 2012. Renal cortical necrosis and acute kidney injury associated with *Plasmodium vivax*: a neglected human parasite. Parasitol. Res. **111**:2213–2216.
110. **Choi HJ, Lee SY, Yang H, Bang JK.** 2004. Retinal haemorrhage in vivax malaria. Trans. R. Soc. Trop. Med. Hyg. **98**:387–389.
111. **Kochar DK, Saxena V, Singh N, Kochar SK, Kumar SV, Das A.** 2005. *Plasmodium vivax* malaria. Emerg. Infect. Dis. **11**:132–134.
112. **Pineros-Jimenez JG, Arboleda M, Jaramillo JC, Blair S.** 2008. Report of five cases of severe neonatal *Plasmodium vivax* malaria in Uraba, Colombia. Biomedica **28**:471–479.
113. **Kochar DK, Das A, Kochar SK, Saxena V, Sirohi P, Garg S, Kochar A, Khatri MP, Gupta V.** 2009. Severe *Plasmodium vivax* malaria: a report on serial cases from Bikaner in northwestern India. Am. J. Trop. Med. Hyg. **80**:194–198.
114. **Metanat M, Sharifi-Mood B.** 2010. Malaria vivax and severe thrombocytopenia in Iran. Iran. J. Parasitol. **5**:69–70.
115. **Alexandre MA, Ferreira CO, Siqueira AM, Magalhaes BL, Mourao MP, Lacerda MV, Alecrim MG.** 2010. Severe *Plasmodium vivax* malaria, Brazilian Amazon. Emerg. Infect. Dis. **16**:1611–1614.
116. **Nayak KC, Mohini Kumar S, Tanwar RS, Kulkarni V, Gupta A, Sharma P, Sirohi P, Ratan P.** 2011. A study on pulmonary manifestations in patients with malaria from northwestern India (Bikaner). J. Vector Borne Dis. **48**:219–223.
117. **Sinha A, Singh G, Bhat AS, Mohapatra S, Gulati A, Hari P, Samantaray JC, Dinda AK, Agaarwasl SK, Bagga A.** Thrombotic microangiopathy and acute kidney injury following vivax malaria. Clin. Exp. Nephrol., in press.
118. **Kute VB, Trivedi HL, Vanikar AV, Shah PR, Gumber MR, Patel HV, Goswami JG, Kanodia KV.** 2012. *Plasmodium vivax* malaria-associated acute kidney injury, India, 2010–2011. Emerg. Infect. Dis. **18**:842–845.
119. **Lacerda MV, Fragoso SC, Alecrim MG, Alexandre MA, Magalhaes BM, Siquiera AM, Ferreira LC, Aroujo JR, Mourao MP, Ferrer M, Castillo P, Martin-Jaular L, Fernandez-Becerra C, del Portillo H, Ordi J, Alonso PL, Bassat Q.** 2012. Postmortem characterization of patients with clinical diagnosis of *Plasmodium vivax* malaria: to what extent does this parasite kill? Clin. Infect. Dis. **55**:e67–e74.
120. **Oh MD, Shin H, Shin D, Kim U, Lee S, Kim N, Choi MH, Chai JY, Choe K.** 2001. Clinical features of vivax malaria. Am. J. Trop. Med. Hyg. **65**:143–146.
121. **Koh KH, Chew PH, Kiyu A.** 2004. A retrospective study of malaria infections in an intensive care unit of a general hospital in Malaysia. Singapore Med. J. **45**:28–36.
122. **Barcus MJ, Basri H, Picarima H, Manyakori C, Sekartuti Elyazar I, Bangs MJ, Maguire JD, Baird JK.** 2007. Demographic risk factors for severe and fatal vivax and falciparum malaria among hospital admissions in northeastern Indonesian Papua. Am. J. Trop. Med. Hyg. **77**:984–991.
123. **Beg MA, Sani N, Mehraj V, Jafri W, Khan MA, Malik A, Menezes E, Hussain R, Smego R, Jr.** 2008. Comparative features and outcomes of malaria at a tertiary care hospital in Karachi, Pakistan. Int. J. Infect. Dis. **12**:37–42.
124. **Sharma A, Khanduri U.** 2009. How benign is benign tertian malaria? J. Vector Borne Dis. **46**:141–144.
125. **Rodriguez-Morales AJ, Ferrer MV, Barrera MA, Pacheco M, Daza V, Franco-Paredes C.** 2009. Imported cases of malaria admitted to two

hospitals of Margarita Island, Venezuela, 1998–2005. Travel Med. Infect. Dis. **7**:44–48.
126. **Lanca EF, Magalhaes BM, Vitor-Silva S, Siqueira AM, Benzecry SG, Alexandre MA, O'Brien C, Bassat Q, Lacerda MV.** 2012. Risk factors and characterization of *Plasmodium vivax*-associated admissions to pediatric intensive care units in the Brazilian Amazon. PLoS One **7**:e35406. doi:10.1371/journal.pone.0035406.
127. **Sharma R, Gohain S, Chandra J, Kumar V, Chopra A, Chatterjee S, Aneja S, Kumar DA.** 2012. *Plasmodium vivax* malaria admissions and risk for mortality in tertiary care children's hospital in north India. Paediatr. Int. Child Health **32**:152–157.
128. **Nurleila S, Syafruddin D, Elyazar IRF, Baird JK.** 2012. Serious and fatal illness associated with falciparum and vivax malaria among patients admitted to hospital at West Sumba in eastern Indonesia. Am. J. Trop. Med. Hyg. **87**:41–49.
129. **Shaikh S, Memon H, Shaikh A, Ahmed I, Iohano B, Baird JK.** 2012. Severe disease in children hospitalized with a diagnosis of *Plasmodium vivax* in south-eastern Pakistan. Malar. J. **11**:144.
130. **Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, Karyana M, Lampah DA, Price RN.** 2008. Multidrug-resistant *Plasmodium vivax* associated with severe and fatal malaria: a prospective study in Papua, Indonesia. PLoS Med. **5**:e128. doi:10.1371/journal.pmed.0050128.
131. **Kochar DK, Tanwar GS, Khatri PC, Kochar SK, Sengar GS, Gupta A, Kochar A, Middha S, Acharya J, Saxena V, Pakalapati D, Garg S, Das A.** 2010. Clinical features of children hospitalized with malaria—a study from Bikaner, northwest India. Am. J. Trop. Med. Hyg. **83**:981–989.
132. **Andrade BB, Reis-Filho A, Souza-Neto SM, Clarencio J, Camargo LM, Barral A, Barral-Netto M.** 2010. Severe *Plasmodium vivax* malaria exhibits marked inflammatory imbalance. Malar. J. **9**:13.
133. **Mahgoub H, Gasim GI, Musa IR, Adam I.** 2012. Severe *Plasmodium vivax* among Sudanese children at New Halfa Hospital, eastern Sudan. Parasites Vectors **5**:154.
134. **Kaushik JS, Gomber S, Dewan P.** 2012. Clinical and epidemiological profiles of severe malaria in children from Delhi, India. J. Health Popul. Nutr. **30**:113–116.
135. **Manning L, Laman M, Law I, Bona C, Aipit S, Teine D, Warrell J, Rosanas-Urgell A, Lin E, Kiniboro B, Vince J, Hwaiwhanje I, Karunajeewa H, Michon P, Siba P, Mueller I, Davis TM.** 2011. Features and prognosis of severe malaria caused by *Plasmodium falciparum*, *Plasmodium vivax* and mixed *Plasmodium* species in Papua New Guinean children. PLoS One **6**:e29203. doi:10.1371/journal.pone.0029203.
136. **Genton B, D'Acremont V, Rare L, Bae K, Reeder JC, Alpers MP, Muller I.** 2008. *Plasmodium vivax* and mixed infections are associated with severe malaria in children: a prospective cohort study from Papua New Guinea. PLoS Med. **5**:e127. doi:10.1371/journal.pmed.0050127.
137. **Poespoprodjo JR, Fobia W, Kenangalem E, Lampah DA, Warikar N, Seal A, McGready R, Sugiarto P, Tjitra E, Anstey NM, Price RN.** 2008. Adverse pregnancy outcomes in an area where multidrug-resistant *Plasmodium vivax* and *Plasmodium falciparum* infections are endemic. J. Infect. Dis. **46**:1374–1381.
138. **Poespoprodjo JR, Fobia W, Kenangalem E, Lampah DA, Hasanuddin A, Warikar N, Sugiarto P, Tjitra E, Anstey NM, Price RN.** 2009. Vivax malaria: a major cause of morbidity in early infancy. Clin. Infect. Dis. **48**:1704–1712.
139. **McGready R, Lee SJ, Wiladphaingern J, Ashley EA, Rijken MJ, Boel M, Simpson JA, Paw MK, Pimanpanarak M, Mu O, Singhasivanon P, White NJ, Nosten FH.** 2012. Adverse effects of falciparum and vivax malaria and the safety of antimalarial drug treatment in early pregnancy: a population-based study. Lancet Infect. Dis. **12**:388–396.
140. **Anstey NM, Russell B, Yeo TW, Price RN.** 2009. The pathophysiology of vivax malaria. Trends Parasitol. **25**:220–227.
141. **Price RN, Douglas NM, Anstey NM.** 2009. New developments in *Plasmodium vivax* malaria: severe disease and the rise of chloroquine resistance. Curr. Opin. Infect. Dis. **22**:430–435.
142. **Russell PF.** 1955. Man's mastery of malaria. Oxford University Press, Oxford, United Kingdom.
143. **Baird JK.** 2000. Resurgent malaria at the millennium: control strategies in crisis. Drugs **59**:719–743.
144. **Rodriguez JC, Uribe GA, Araujo RM, Narvaez PC, Valencia SH.** 2011. Epidemiology and control of malaria in Colombia. Mem. Inst. Oswaldo Cruz **106**(Suppl 1):114–122.
145. **Carrara VI, Sirilak S, Thonglairuam J, Rojanawatsirivet C, Proux S, Gilbos V, Brockman A, Ashley EA, McGready R, Krudsood S, Leemingsawat S, Looareesuwan S, Singhasivanon P, White N, Nosten F.** 2006. Deployment of early diagnosis and mefloquine-artesunate treatment of falciparum malaria in Thailand: the Tak Malaria Initiative. PLoS Med. **3**:e183. doi:10.1371/journal.pmed.0030183.
146. **Park JW, Jun G, Yeom JS.** 2009. *Plasmodium vivax* malaria: status in the Republic of Korea following reemergence. Korean J. Parasitol. **47**(Suppl):S39–S50.
147. **Baird JK.** 2012. Reinventing primaquine for endemic malaria. Expert Opin. Emerg. Drugs **17**:439–444.
148. **Baird JK.** 2012. Elimination therapy for the endemic malarias. Curr. Infect. Dis. Rep. **14**:227–237.
149. **Baird JK.** 2012. Tropical health sustainability, p 11134–11163. *In* Meyers RA (ed), Encyclopedia of sustainability science and technology. Springer Verlag, New York, NY.
150. **Jensen JB, Trager W.** 1976. Human malaria parasites in continuous culture. Science **193**:673–675.
151. **Rubach MP, Mukemba J, Florence S, John B, Crookston B, Lopansri BK, Yeo TW, Piera KA, Alder SC, Weinberg JB, Anstey NM, Granger DL, Mwaikambo ED.** 2012. Plasma *Plasmodium falciparum* histidine-rich protein-2 concentrations are associated with malaria severity and mortality in Tanzanian children. PLoS One **7**:e35985. doi:10.1371/journal.pone.0035985.
152. **Silamut K, White NJ.** 1993. Relation of the stage of parasite development in the peripheral blood to prognosis in severe falciparum malaria. Trans. R. Soc. Trop. Med. Hyg. **87**:436–443.
153. **Dondorp AM, Desakorn V, Pongtavornpinyo W, Sahassananda D, Silamut K, Chotivanich K, Newton PR, Pitisuttithum P, Smithyman AM, White NJ, Day NP.** 2005. Estimation of the total parasite biomass in acute falciparum malaria from plasma PfHRP2. PLoS Med. **2**:e204. doi:10.1371/journal.pmed.0020204.
154. **Hanson J, Lam SW, Mahanta KC, Pattnaik R, Alam S, Mohanty S, Hasan MU, Hossain A, Charunwatthana P, Chotivanich K, Maude RJ, Kingston H, Day NP, Mishra S, White NJ, Dondorp AM.** 2012. Relative contributions of macrovascular and microvascular dysfunction to disease severity in falciparum malaria. J. Infect. Dis. **206**:571–579.
155. **Minigo G, Woodberry T, Piera KA, Salwati E, Tjitra E, Kenangalem E, Price RN, Engwerda CR, Anstey PM, Plebanski M.** 2009. Parasite-dependent expansion of TNF receptor II-positive regulatory T cells with enhanced suppressive activity in adults with severe malaria. PLoS Pathog. **5**:e1000402. doi:10.1371/journal.ppat.1000402.
156. **Sherry BA, Alava G, Tracey KJ, Martiney J, Cerami A, Slater AF.** 1995. Malaria-specific metabolite hemozoin mediates the release of several potent pyrogens (TNF, MIP-1 alpha and MIP-1 beta) in vitro, and altered thermoregulation in vivo. J. Inflamm. **45**:85–96.
157. **Marsh K, Forster D, Waruiru C, Mwangi I, Winstanely M, Marsh V, Newton C, Winstanley P, Warn P, Peshu N, Pasvol G, Snow R.** 1995. Indicators of life-threatening malaria in African children. N. Engl. J. Med. **332**:1399–1404.
158. **Miller LH, Baruch DI, Marsh K, Doumbo OK.** 2002. The pathogenic basis of malaria. Nature **415**:673–679.
159. **Kirchgatter K, del Portillo HA.** 2005. Clinical and molecular aspects of severe malaria. Ann. Braz. Acad. Sci. **77**:455–475.
160. **Miller LH, Good MF, Milon G.** 1994. Malaria pathogenesis. Science **264**:1178–1183.
161. **Costa FT, Lopes SC, Ferrer M, Leite JA, Martin-Jaular L, Bernabeu M, Nogueira PA, Mourao MP, Fernandez-Becerra C, Lacerda MV, del Portillo H.** 2011. On cytoadhesion of *Plasmodium vivax*: raison d'etre? Mem. Inst. Oswaldo Cruz **106**(Suppl 1):79–84.
162. **Genrich GL, Guarner J, Paddock CD, Shieh WJ, Greer PW, Barnwell JW, Zaki SR.** 2007. Fatal malaria infection in travelers: novel immunohistochemical assays for the detection of *Plasmodium falciparum* in tissues and implications for pathogenesis. Am. J. Trop. Med. Hyg. **76**:251–259.
163. **Suwanarusk R, Cooke BM, Dondorp AM, Silamut K, Sattabongkot J, White NJ, Udomsangpetch R.** 2004. The deformability of red blood cells parasitized by *Plasmodium falciparum* and *P. vivax*. J. Infect. Dis. **189**:190–194.
164. **Handayani S, Chiu DT, Tjitra E, Kuo JS, Lampah D, Kenangalem E, Renia L, Snounou G, Price RN, Anstey NM, Russell B.** 2009. High deformability of *Plasmodium vivax*-infected red blood cells under microfluidic conditions. J. Infect. Dis. **199**:445–450.
165. **Chamberlain JK, Lichtman MA.** 1978. Marrow cell egress: specificity of the site of penetration into the sinus. Blood **52**:959–968.
166. **Yoeli M.** 1948. Non-pigmented malaria parasites in the bone marrow

from a mixed infection of leishmania and plasmodium vivax. Trans. R. Soc. Trop. Med. Hyg. **42**:99.
167. **Ru YX, Mao BY, Zhang FK, Pang TX, Zhao SX, Liu JH, Wickramasinghe SN.** 2009. Invasion of erythroblasts by *Plasmodium vivax*: a new mechanism contributing to malarial anemia. Ultrastruct. Pathol. **33**: 236–242.
168. **Imirzalioglu C, Soydan N, Schaller M, Bretzel RG, Chakraborty T, Domann E.** 2006. Diagnosis of mixed *Plasmodium malariae* and *P. vivax* infection in a development aid volunteer by examination of bone-marrow specimens by real-time PCR. J. Clin. Microbiol. **44**:2307–2310.
169. **O'Donnell J, Goldman JM, Wagner K, Ehinger G, Martin N, Leahy M, Kariuki N, Dokal I, Roberts I.** 1998. Donor-derived *Plasmodium vivax* infection following volunteer unrelated bone marrow transplantation. Bone Marrow Transplant. **21**:313–314.
170. **Panichakul T, Sattabongkot J, Chotivanich K, Sirichaisinthop J, Cui L, Udomsangpetch R.** 2007. Production of erythropoietic cells in vitro for continuous culture of *Plasmodium vivax*. Int. J. Parasitol. **37**:1551–1557.
171. **Wickramasinghe SN, Abdalla SH.** 2000. Blood and bone marrow changes in malaria. Baillieres Best Pract. Res. Clin. Haematol. **13**:277–299.
172. **del Portillo HA, Lanzer M, Rodriquez-Malaga S, Zavala F, Fernadez-Becerra C.** 2004. Variant genes and the spleen in *Plasmodium vivax* malaria. Int. J. Parasitol. **34**:1547–1554.
173. **Imbert P, Rapp C, Buffet PA.** 2009. Pathological rupture of the spleen in malaria: analysis of 55 cases (1958–2008). Travel Med. Infect. Dis. **7**:147–159.
174. **Anderson F, Douglas NM, Bustos D, Galappaththy G, Qi G, Hsiang MS, Kusriastuti R, Mendis K, Taleo G, Whittaker M, Price RN, von Seidlin L.** 2011. Trends in malaria research in 11 Asian Pacific countries: an analysis of peer-reviewed publications over two decades. Malar. J. **10**:131. doi:10.1186/1475-2875-10-131.
175. **Siqueira AM, Magalhaes BM, Melo GC, Ferrer M, Castillo P, Martin-Jaular L, Fenandez-Becerra C, Ordi J, Martinez A, Larcerda MVG, del Portillos HA.** 2012. Spleen rupture in a case of untreated *Plasmodium vivax* infection. PLoS Negl. Trop. Dis. **6**(12):e1934. doi:10.1371/journal.pntd.0001934.



Kevin Baird trained in microbiology, biochemistry, protozoology, epidemiology, and parasitology at the University of Maryland (B.Sc., M.Sc.) and Tulane University (Ph.D.). After working at the Walter Reed Army Institute of Research, he embarked upon a 22-year career on active duty in the U.S. Navy Medical Service Corps, conducting laboratory, field, and clinical research on vivax malaria, principally in Indonesia. He now resides permanently in Jakarta, where he directs the Eijkman-Oxford Clinical Research Unit on behalf of the University of Oxford and the Eijkman Institute of Molecular Biology. Having contracted *P. falciparum* and *P. vivax* each on several occasions in the long course of this work, and having firmly considered the latter a consistently far more sickening experience, he has long harbored skepticism regarding the presumably harmless nature of vivax malaria. Those experiences spurred the somewhat prolonged examination and consideration of "benign" vivax malaria summarized in this review.