Unstable Malaria Transmission in the Southern Peruvian Amazon and Its Association with Gold Mining, Madre de Dios, 2001–2012

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Abstract. The reemergence of malaria in the last decade in Madre de Dios, southern Peruvian Amazon basin, was accompanied by ecological, political, and socioeconomic changes related to the proliferation of illegal gold mining. We conducted a secondary analysis of passive malaria surveillance data reported by the health networks in Madre de Dios between 2001 and 2012. We calculated the number of cases of malaria by year, geographic location, intensity of illegal mining activities, and proximity of health facilities to the Peru–Brazil Interoceanic Highway. During 2001–2012, 203,773 febrile cases were identified in Madre de Dios, of which 30,811 (15.1%) were confirmed cases of malaria; all but 10 cases were due to *Plasmodium vivax*. Cases of malaria rose rapidly between 2004 and 2007, reached 4,469 cases in 2005, and then declined after 2010 to pre-2004 levels. Health facilities located in areas of intense illegal gold mining reported 30-fold more cases than those in non-mining areas (ratio = 31.54, 95% confidence interval [CI] = 19.28, 51.60). Finally, health facilities located > 1 km from the Interoceanic Highway reported significantly more cases than health facilities within this distance (ratio = 16.20, 95% CI = 8.25, 31.80). Transmission of malaria in Madre de Dios is unstable, geographically heterogeneous, and strongly associated with illegal gold mining. These findings highlight the importance of spatially oriented interventions to control malaria in Madre de Dios, as well as the need for research on malaria transmission in illegal gold mining camps.

BACKGROUND

Malaria is a reemerging vector-borne infection endemic in more than 104 countries in tropical and subtropical areas,^{1,2} and represents a major cause of morbidity and mortality³ and economic loss worldwide.⁴ It is a persistent public health problem in Latin America,^{5,6} where the predominant etiologic agent is *Plasmodium vivax* (80%),⁶ a traditionally neglected, yet potentially severe pathogen, which has a unique ability to relapse.^{7,8} The vast majority of cases in Latin America are concentrated in the Amazon region (90%).^{9,10} Peru has the third highest number of malaria cases in South America,⁶ with significant health¹¹ and economic¹² impacts. Despite decades of control efforts,¹³ malaria remains endemic in the Peruvian Amazon, and has resurged in recent years,¹¹ posing a significant threat to public health.

Malaria transmission in the Amazon is promoted by several factors: anthropogenically-driven habitat change—for example, agriculture, logging, and mining—resulting in changes in vector breeding sites including urbanization^{14,15}; immigration of nonimmune humans into rural settlements in new frontier sites^{16,17}; and asymptomatic carriers.¹⁸ Gold mining leads to several of these conditions, including habitat modification^{19,20} and human settlements in the Amazon frontier. In this sense, illegal gold mining may be especially important, given its unregulated nature, and the poor working, living, and health conditions associated with this activity.²¹ Therefore, control strategies may face additional challenges in areas with certain specific high-risk groups, such as illegal miners,^{22,23} and these unique hotspots may be critical for the overall success of

malaria eradication.²⁴ Despite the potential role of illegal gold mining in malaria transmission in the Amazon, the relation between illegal gold mining and malaria transmission is unclear.

The epidemiology of malaria in the Peruvian Amazon has been studied almost exclusively in non-mining settings in the northern Amazon basin. Our understanding of the potential impact of illegal gold mining elsewhere in Peru is more limited, but is essential for understanding malaria epidemiology in Peru vis-à-vis control and elimination measures. Madre de Dios (Mdd), an endemic region in the southern Peruvian Amazon, has gold mining as its main economic activity, contributing over 80% of the annual national gold production,^{25,26} the vast majority of which is illegal (99%).²⁵ At the same time, Mdd has the third largest number of malaria cases in Peru for several years,²⁷ despite being the least populated region in Peru. Several malaria outbreaks have occurred in Mdd,²⁸ paralleling the recent increases illegal mining activities and gold prices. In 2011, the Peruvian government issued strict legislation penalizing illegal mining and started interdiction activities in Mdd, including confiscation and destruction of illegal mining machinery, local fuel taxation, and restriction in the distribution of mercury and cyanide. Interdiction activities aroused violent protests from illegal miners, including strikes and road blocks requiring military intervention, and have resulted in four deaths and erratic illegal mining activities. In addition, the environmental changes brought by the construction of the Interoceanic Highway beginning in 2006, which connects the Brazilian Amazon to the Peruvian coastline, may have also resulted in changes in Mdd malaria epidemiology.

In this context, we used a combination of different methods to describe the epidemiology of malaria in Mdd and its potential association with illegal gold mining. The study had two main components: 1) a secondary analysis of the malaria surveillance data from the Regional Health Directorate of Mdd between 2001 and 2012 and 2) a detailed case data

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review from field visits to selected health facilities in the areas of intense illegal gold mining in MdD.

METHODS

Study design and context. MdD, located in the southern Peruvian Amazon basin, has an area of 85,300 km² with a population of 109,555 inhabitants, over one quarter of who live in rural areas.²⁹ This department is composed of three provinces (Tambopata, Manu, and Tahuamanu) and 11 districts. MdD has a tropical climate with heavy rainfall between December and March (mean annual precipitations between 1,758 and 2,806 mm).²⁸

The Peruvian Ministry of Health's General Directorate of Epidemiology has carried out a passive surveillance system for diseases of mandatory reporting on a country-wide basis, including malaria, since 1994. Reporting of all malaria cases is mandatory across the > 8,000 health facilities in Peru, using official, standardized reporting documents. Case confirmation requires clinical and epidemiologic data (exposure history in endemic areas) plus a positive blood smear. The number of confirmed malaria cases is reported by the individual health facilities to health networks, which in turn forward the report to the Regional Health Directorates and then to the General Directorate of Epidemiology.³⁰ Confirmed cases of *P. vivax* malaria are reported weekly in an aggregate fashion, whereas confirmed cases of *Plasmodium falciparum* malaria are reported immediately and individually. Malaria surveillance data are routinely collected by 109 health facilities in MdD organized in 10 health networks, mainly in the primary care facilities where most of the cases are seen. Figure 1 shows the area of responsibility of the health networks in 2001 and 2012.

Gold mining in MdD dates back to the early 1900s but consisted mainly of small-scale manual extraction limited to remote, inner areas of Huepetuhe, Mazuko, and Colorado in the Colorado River. Larger mining settlements in Huepetuhe and Colorado between 1970 and 1980 marked the expansion of mining activities that intensified in the 1980s with semi-mechanized extraction techniques. Camps surrounding the current Interoceanic Highway were established later in Laberinto, Inambari, and Tambopata. Between 1990 and 2005, mining further expanded with the use of heavy machinery and Huepetuhe consolidated as the main area. The rise of gold prices after 2005 preceded the out-of-control growth of illegal gold mining in MdD, and the construction of the Interoceanic Highway may have facilitated this expansion. Mining settlements have proliferated exponentially since, reaching national reserves near the Interoceanic Highway.³¹

Data. Annual malaria reports between 2001 and 2012 were obtained from the MdD Regional Directorate of Health. These reports included weekly counts of febrile patients identified and tested for malaria. Malaria cases by age groups and the name/location of cases were aggregated by health facility location. Gender, pregnancy, and malaria therapy data were incomplete and analyzed when available. The proximity of each health facility in MdD to the Interoceanic Highway was determined using geographic information systems mapping.³² The MdD contribution of malaria cases in relation to the total number of cases reported in Peru was based on country-wide data available in the General Epidemiology Directorate website.²⁸

To supplement surveillance data, primary data were collected during field supervision visits to each health facility in the high-intensity gold mining areas and those located near the Interoceanic Highway, as part of the activities of the

FIGURE 1. Health networks in Madre de Dios and their capture areas in 2001 (108 health facilities) and 2012 (120 health facilities). Areas of intense illegal gold mining included those served by the health networks of Colorado, Huepetuhe, Mazuko, and Laberinto. Health facilities near the Interoceanic Highway were defined as those in a radius less than 1 km around the Interoceanic Highway.

Amazonian International Center of Excellence for Malaria Research. These data included all febrile and malaria cases reported, and were collected from the laboratory registry in each health facility.

Monthly climate data between 2001 and 2012 were obtained from an international meteorological forum that collects daily climatic data from three meteorological stations in MdD.³³ Data for analysis included maximal, minimal, and mean monthly temperatures (°C), and total monthly rainfall (mm).

Finally, data on monthly gold extraction in MdD were obtained from the Peruvian Ministry of Energy and Mining.³⁴ International average monthly gold prices were obtained from the World Gold Council.³⁵

Statistical analyses. Trends and differences in the total number of malaria cases were analyzed by month and region. Health facilities were grouped using two separate and overlapping classifications to highlight two different aspects of malaria transmission: mining versus non-mining areas and inner versus Interoceanic Highway areas. The Colorado, Huepetuhe, Mazuko, and Laberinto health networks are located in mining areas. The Interoceanic Highway goes through health facilities of the Mazuko, Laberinto, Tambopata, Tahuamanu, Iberia, Las Piedras, and Iñapari health networks. Given the high mobility of a large proportion of the population in MdD, we anticipated that census estimates and projections of the size of the populations served by each health network would be unreliable and potentially misleading in areas of intense migration due to mining activities. Thus, we opted to carry out epidemiologic analyses using the absolute number of malaria cases, instead of calculating incidence rates adjusted by the population size. Malaria case counts were analyzed as the dependent variable with a generalized linear regression model to estimate risk ratios by quarter, year, geographic region, intensity of gold mining activities in the area, and proximity of each health facility to the Interoceanic Highway. The goodness-of-fit χ^2 statistic was used to determine fit to a Poisson model; the modified likelihood-ratio test evaluated whether overdispersion was present. Therefore, we used a negative binomial regression model to account for overdispersion by incorporating it into the model.³⁶ The Vuong's test was used to determine if there was a better fit using a zero-inflated negative binomial model instead of a conventional negative binomial model.³⁷ Descriptive analysis of short-time trends in specific facilities was also conducted to identify potential outbreaks. Finally, Spearman correlation coefficients (ρ_s) were calculated between the monthly number of malaria cases and the 1-month lagged climatic and gold price/extraction variables. All statistical analyses were conducted using Stata version 11.2 (StataCorp LP, College Station, TX).

Research ethics. This study was approved by the Institutional Review Board of the U.S. Naval Medical Research Unit 6, and administratively approved by the MdD Regional Health Directorate.

RESULTS

From January 2001 to December 2012, a total of 203,773 febrile cases were reported in MdD, of which 30,811 (15%) were confirmed to be malaria. All cases but 10 (< 0.1%) were due to *P. vivax*. Two cases of *P. falciparum* malaria presented in the non-mining areas of the Iberia district in 2006 and 2008, apparently introduced from Brazil or Bolivia,

and without resulting in detectable further transmission. Cases were predominantly male, and 28 years old on average (Table 1). Few (< 1%) cases of malaria in pregnant women were reported. No malaria-related fatalities were reported. Nearly 95% of the confirmed cases were reported to have received treatment, but over 90% of treatment provided was unsupervised, especially in the illegal gold mining areas. Miners often live far from health facilities and receiving supervised treatment daily would imply loss of daily wages and hefty transportation expenses. Directly observed therapy is limited to non-miner residents of towns, where health facilities are located.

Nearly, all cases of malaria (93%) were found in the health networks in the province of Manu primarily in three areas: Colorado (56%), Huepetuhe (25%), and Mazuko (12%). These health networks, in addition to the health network of Laberinto, serve areas where illegal gold mining activities take place, and reported > 30 times more malaria cases than health networks serving areas of low gold mining activities (case count ratio = 31.54, 95% confidence interval [CI]: 19.28, 51.60, $P < 0.001$), and this difference was continuously present across the study period ($P = 0.572$, Figure 2A). Health facilities in inner areas located far from the Interoceanic Highway (≥ 1 km) reported significantly more malaria cases than health facilities close to the highway (ratio = 16.20, 95% CI = 8.25, 31.80, $P < 0.001$, Figure 2B).

The relationship between location of health facilities in proximity to the Interoceanic Highway and malaria cases was confirmed during field visits. Facilities reporting most malaria close to the Interoceanic Highway in areas of high-intensity illegal gold mining primarily had isolated malaria outbreaks lasting for up to 4 months (Figure 3) involving up to 176 cases. Health personnel anecdotally reported cases were due to migration of miners from malaria-endemic areas of MdD. In between outbreaks, these facilities mostly presented no or very few malaria cases. In comparison, facilities away from the highway presented continuous, year-long transmission. Population size did not seem to explain these differences in transmission (data not shown). The sporadic, small malaria outbreaks near the Interoceanic Highway that never grew

TABLE 1

Characteristics of patients with confirmed malaria diagnosis, Madre de Dios, 2001–2012

Characteristics	N	%
Causative agent		
<i>Plasmodium vivax</i>	30,802	99.9
<i>Plasmodium falciparum</i>	3	< 0.1
Mixed	7	< 0.1
Age (years)*	28.3 ± 13.6	
Gender†		
Male	7,195	81.0
Female	1,690	19.0
Malaria in pregnancy‡	167	0.9
Treated cases‡	18,038	94.4
Quarter		
First quarter	9,618	31.3
Second quarter	7,363	24.0
Third quarter	6,362	20.7
Fourth quarter	7,348	23.9

*Mean ± standard deviation, otherwise N (%).

†Information on gender was only included in the 2006 and 2007 annual malaria reports (N = 8,885).

‡Information on malaria in pregnancy began to be included in the annual malaria reports in 2007 (N = 19,119).

FIGURE 2. Annual number of cases of *Plasmodium vivax* malaria by the (A) intensity of illegal gold mining activities and (B) proximity to the Interoceanic Highway, Madre de Dios, 2001–2012. Areas of intense illegal gold mining included those served by the health networks of Colorado, Huepetuhe, Mazuko, and Laberinto (A). Health facilities near the Interoceanic Highway were defined as those in a radius less than 1 km around the Interoceanic Highway (B).

to full epidemics as opposed to the inner mining area of Huepetuhe and Delta-1 highlight the heterogeneity of malaria transmission in this region.

The annual cases of malaria in MdD increased rapidly between 2004 and 2007, peaked in 2005 with 4,469 cases and then declined annually until reaching 2001 levels in 2012 ($P = 0.836$, Poisson regression). The health network of Colorado in Manu Province drove the greatest part of this increase, accounting for 93% of the cases between 2004 and 2012, displacing the Mazuko and Huepetuhe health network, which had reported most cases between 2001 and 2003 (Supplemental Table 1). The importance of MdD in malaria transmission within Peru changed from 2001 to 2003, initially ranking 12th/13th in annual malaria cases, accounting for < 1% of the total in Peru, then moving to second/third place from 2004 to 2010, when MdD accounted for 6–12% of the annual case burden. From 2011 onwards, MdD was fourth/fifth place, accounting for 2% of annual malaria cases in Peru.

Malaria cases were seasonal ($P = 0.020$, data not shown) with 37% more cases between January and March compared with the rest of the year (95% CI = 4–80%, $P = 0.023$). No

differences were noted among the second, third, and fourth quarters ($P = 0.615$). No association was found between monthly cases and the 1-month lagged rainfall as obtained from MdD meteorological data (Figure 4), nor mean temperature ($\rho_s = 0.11$, $P = 0.222$), minimal temperature ($\rho_s = 0.16$, $P = 0.070$), maximal temperature ($\rho_s = 0.11$, $P = 0.226$), or total monthly rainfall ($\rho_s = 0.11$, $P = 0.176$).

The monthly number of malaria cases was strongly associated with the amount of gold extracted in the previous month in MdD ($\rho_s = 0.32$, $P < 0.001$, Figures 5 and 6), but only weakly with the average gold prices in the previous month in Peru ($\rho_s = 0.18$, $P = 0.022$, Figures 5 and 6). When the association between the number of malaria cases and the 1-month lagged gold extraction was evaluated using Spearman's correlation, we found a positive and significant association between the 1-month lagged amount of monthly gold extraction in MdD and the number of cases of *P. vivax* malaria (Figure 6A).

FIGURE 3. *Plasmodium vivax* malaria in selected health facilities from high-intensity illegal gold mining areas in Madre de Dios, 2001–2013.

FIGURE 4. *Plasmodium vivax* malaria, temperature, and rainfall in Madre de Dios, 2001–2012. Spearman rank correlations (ρ_s) refer to the associations between the 1-month lagged climatic parameters and the number of malaria cases. $T_{\min}$ = minimum temperature; T_{mean} = mean temperature; T_{max} = maximum temperature.

FIGURE 5. *Plasmodium vivax* malaria, gold prices, and gold extraction in Madre de Dios, 2001–2012. Spearman rank correlations (ρ_s) refer to the association between the 1-month lagged gold price/extraction and the number of malaria cases.

We found a significant curvilinear association between 1-month lagged gold prices and the number of malaria cases, which had an inverted “U” shape (Figure 6B). Both low and high gold prices resulted in lower number of malaria cases. Instability in the amount of gold extracted from MdD is apparent from 2011 onward, after the Peruvian government implemented increased interdiction activities against illegal mining. The diminished intensity of mining activities probably contributed to the reduction in malaria reported between 2011 and 2012, as cases started dropping in 2011 (Figure 5).

DISCUSSION

We observed that the transmission of *P. vivax* malaria in MdD is highly unstable, with the occurrence of frequent and large epidemics. Notably, the incidence of malaria was strongly with the quantities of gold extracted in the region. Malaria transmission was epidemic and concentrated in areas of intense illegal gold mining, with over 30 times the number of malaria cases than the health networks serving areas of mild illegal gold

mining. Elsewhere, malaria transmission appeared to follow a more stable low-level endemic pattern. Malaria transmission was very low in areas nearby the Intercoceanic Highway, with occasional outbreaks only. These findings have important implications for malaria control in MdD, given that unstable malaria is associated with low rates of naturally acquired immunity in the population, which would be predicted to favor the occurrence of outbreaks and appearance of cases with greater severity.³⁸ These patterns of malaria transmission requires individualized public intervention approaches.^{38,39}

The reasons explaining the unstable transmission of *P. vivax* malaria in MdD remain unclear, but illegal gold mining volume was significantly correlated to malaria transmission in MdD and mining activities seem to have played a role in other regions in the Amazon.^{40–43} Several mechanisms may underlie the association between gold mining and malaria. First, mining activities lead to deforestation and human modification of the environment,^{19,20} both of which have been linked to increased number of cases of malaria by altering vector breeding sites and affecting vector abundance, composition, and behavior.¹⁴ Second, gold mining in MdD is associated with immigration of non-immune itinerant workers from the low-endemicity southern Andean regions of Peru,^{25,26} who work and live in precarious conditions, with limited access to health care and any preventive measures against malaria.²⁶ Others have suggested that the mercury toxicity may be associated with an increased immunologic susceptibility to malaria,⁴⁴ and exposure to mercury during gold mining has been associated with malaria prevalence,⁴⁵ although the potential causality of this association is still unclear. Increased levels of mercury⁴⁶ and mercury genotoxicity were observed in illegal gold miners from MdD and Peru overall,⁴⁷ but this theory still requires further empiric validation.

Climate has been postulated as a driving force for the changing (expanding) epidemiology of malaria. There is evidence that climate, including the El Niño Southern Oscillation, is associated with malaria transmission in the Amazon basin,⁴⁸ and specifically in Peru.⁴⁹ However, no significant associations were found between the monthly reported number of cases and the climatic variables studied in a straightforward analysis, particularly local rainfall and temperature. More sophisticated 3analysis may reveal more complex associations between weather and malaria emergence in MdD, but so far our

FIGURE 6. Correlation between the number of cases of *Plasmodium vivax* malaria, gold prices, and gold extraction in Madre de Dios, 2001–2012. ρ_s = Spearman's correlation coefficient.

results again brings focus back on the association of malaria with illegal gold mining independent of these abiotic factors. Mining-related deforestation could have played a role, but may have not prevented the disappearance of malaria from the region. Drug logistics may have also contributed to malaria transmission, as remote facilities lack temperature-controlled environments to prevent degradation. Also, limited access to health care and high population mobility prevents complete directly observed therapy and treatment was often prescribed for self-administration under no supervision. Finally, drug shortages have probably contributed to greater malaria transmission. While several favorable conditions related to the host, parasite, vector, and environment converge to determine *P. vivax* transmission; it is unclear why these conditions do not ultimately lead to sustained malaria transmission. The development of clinical immunity (asymptomatic parasitemia leading to mosquito infection) could partially explain the disappearance of the malaria epidemics, but empirical data is lacking. Regarding gold production, the decline in the number of reported cases of malaria was paralleled by a period of instability in gold extraction from MdD, beginning in 2011. This is probably the result of the interdiction activities against illegal mining, which resulted in diminished and erratic mining and gold output.

Significant geographic heterogeneity was evident, even among areas of intense illegal gold mining. Microgeographic clustering of malaria has been previously identified in the northern Peruvian Amazon, where gold mining activities are minimal.^{50,51} This spatial heterogeneity has been linked to the location of vector breeding sites and clustering of human reservoirs.²⁴ In our study, proximity to the Intercoceanic Highway was associated with a lower risk for malaria transmission, which may be related to the destruction of vector breeding site. Future studies of vector behavior and distribution may provide important clues as to the patchy distribution of malaria in MdD. In the light of the spatial heterogeneity of malaria transmission in MdD, control strategies should be spatially oriented,⁵² and directed toward specific hotspots of malaria transmission, rationalizing the allocation of resources.²⁴ Illegal gold mining camps may constitute an attractive target for such interventions, but further individual-level studies are needed to understand the factors underlying the high-level and heterogeneous transmission of malaria in illegal gold mining camps.⁵³

Several limitations should be taken into consideration when interpreting the results of this study, most of which stem from reliance on passive surveillance data and the lack of systematically obtained environmental data. First, the case information may have been affected by underreporting and/or misclassification. To limit potential biases resulting from including non-cases in the analysis, given the low specificity of the definition of “probable cases” of malaria in endemic settings, we restricted all analyses to confirmed cases. However, this approach may have still yielded an underestimation of the true regional malaria burden, due to the detection limit of microscopy and care-seeking outside MoH facilities, primarily in informal private pharmacies. In addition, the uncontrolled sale of antimalarials may have resulted in subtherapeutic treatment and led to further asymptomatic malaria, worsening the underestimation of the true incidence of malaria. Nevertheless, because case identification and reporting procedures did not change over the study period, it is unlikely that the

observed trends and distribution of malaria cases are affected by this exclusion criterion. Second, only general sociodemographic and clinical data related to malaria cases of malaria were available, with an absence of other relevant variables (such as number of previous malaria episodes, travel/residence history, use of prevention measures, occupational history related to gold mining). In addition, incomplete data were available for several years and health networks. Although these shortcomings necessarily mean that the causes behind the reported associations remain speculative, we believe that the study’s hypothesis-generation approach contributes valuable evidence about the changing epidemiology of malaria in MdD and its association with illegal gold mining, particularly considering the paucity of information in this area. Moreover, the obligatory nature of the notification of cases of malaria and the inclusion of all health networks in MdD argues for the representativeness of the data. Also, health facilities often lack microscopes or trained microscopists and the high mobility of miners leads them to be referred to or seek care in better-suited facilities away from their work or residence area, further distorting geographic incidence rates. Finally, the passive nature of the malaria surveillance system required that all malaria cases were symptomatic, and could not gather any information on asymptomatic malaria, although previous preliminary reports have noted that the frequency of asymptomatic cases is low in the region.³⁹

Despite these limitations, identification of an unstable and geographically heterogeneous pattern of malaria transmission in MdD, with high levels of transmission in areas of intense illegal gold mining, has important potential implications for malaria control and elimination. Another important issue for malaria elimination programs is the need for spatially oriented, targeted control measures, and our findings suggest that areas of illegal gold mining may constitute an important target for such interventions. However, further research of the dynamics of malaria transmission in illegal gold mining camps is critical to confirm our findings. The limited access to health care and preventive measures, widespread unsupervised therapy with drugs of questionable quality, and the high mobility of illegal gold miners in MdD may favor the dissemination of malaria to nonendemic areas with the potential of inducing malaria epidemics and preventing elimination in this Peruvian region and the Amazon Basin overall.

In conclusion, transmission of malaria in MdD is unstable, geographically heterogeneous, and strongly associated with illegal gold mining activities, and transmission in this type of settings is a major bottleneck for malaria elimination in the Amazon Basin. These findings highlight the importance of spatially oriented interventions to control malaria in MdD, as well as the need for research regarding the vector behavior and distribution, as well as the factors potentially associated with heightened malaria transmission in illegal gold mining camps. The high mobility, poor access to health care, frequently unsupervised treatment, and access to drugs of variable quality that characterized workers in illegal gold mining camps constitute a serious and imminent threat for the dissemination of malaria epidemics to other nonendemic areas.

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