

# Chloroquine-Resistant Malaria in Travelers Returning from Haiti after 2010 Earthquake

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We investigated chloroquine sensitivity to *Plasmodium falciparum* in travelers returning to France and Canada from Haiti during a 23-year period. Two of 19 isolates obtained after the 2010 earthquake showed mixed *pfcr76K+T* genotype and high 50% inhibitory concentration. Physicians treating malaria acquired in Haiti should be aware of possible chloroquine resistance.

In Haiti (2011 population  $\approx$ 9.7 million), malaria is endemic. Approximately 30,000 malaria infections are confirmed annually among  $\approx$ 200,000 estimated malaria cases, mainly *Plasmodium falciparum* infections (1). On January 12, 2010, a 7.0 magnitude earthquake struck Haiti near Port-au-Prince, leaving much of the population homeless.

The main malaria vector in Haiti, *Anopheles albimanus* mosquitoes, which mostly bite outdoors during November–January, placed evacuees at high risk for infection (2,3).

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Severe flooding after hurricane Tomas in November 2010 probably compounded the problem by facilitating parasite reservoirs and mosquito breeding (4). Some studies suggest that these events might have increased malaria transmission in Haiti. Two observational surveys, 1 performed by a mobile medical team during March–April 2010 (5) and 1 during November 2010–February 2011 in a primary care clinic in Leogane (6), reported a high proportion of malaria infection among persons with fever (20.3% and 46.9%, respectively) compared with reports from a population-based survey in 2006 (14.2%) (2). The US National Malaria Surveillance System reported a 3-fold increase in malaria among travelers returning from Haiti in 2010 (170 cases) compared with 2009 (58 cases) (7).

Chloroquine associated with primaquine since 2009, is the recommended first-line treatment for uncomplicated malaria. In vitro and molecular surveillance data collected during the past 2 decades suggest continued *P. falciparum* sensitivity to chloroquine (3,8,9). However, a 2006–2007 study in Artibonite Valley, Haiti, showed the chloroquine resistance-associated *Pfcr76T* genotype in  $\approx$ 6% (5/79) of *P. falciparum* isolates, although clinical data were lacking (10). Subsequently, the Haitian Ministry of Health acknowledged that routine chloroquine efficacy surveillance should be reinforced (11). We investigated the chloroquine sensitivity of *P. falciparum* parasites isolated from travelers recently returned from Haiti to Canada and France by using genotypic and phenotypic methods.

## The Study

We collected retrospective data from the National Malaria Reference Centre (Paris, France) and Public Health Ontario (Toronto, ON, Canada) during 1988–2010 and 2007–2010, respectively. *P. falciparum* infection was considered probably acquired in Haiti if biologically confirmed by thin and thick blood smears from persons who had recently traveled to Haiti in the 2 months before infection was diagnosed. Basic demographic and epidemiologic data, clinical and parasitologic information, treatment, and history of travel and *P. falciparum* infection were collected systematically. Forty of 80 participating hospitals in the sentinel network in France also documented resistance to antimalarial drugs. Pretreatment isolates were collected to determine chloroquine susceptibility by molecular analysis of the *Pfcr76* locus and by comparing the ratio of in vitro chloroquine response of the clinical isolate with a chloroquine-sensitive reference clone.

Seventy-nine imported *P. falciparum* infections were recorded: 49 before the earthquake (all in France) and 30 after the earthquake (3 in Canada and 27 in France). The

<sup>1</sup>Members of the French National Reference Center for Imported Malaria Study who contributed data are listed at the end of this article.

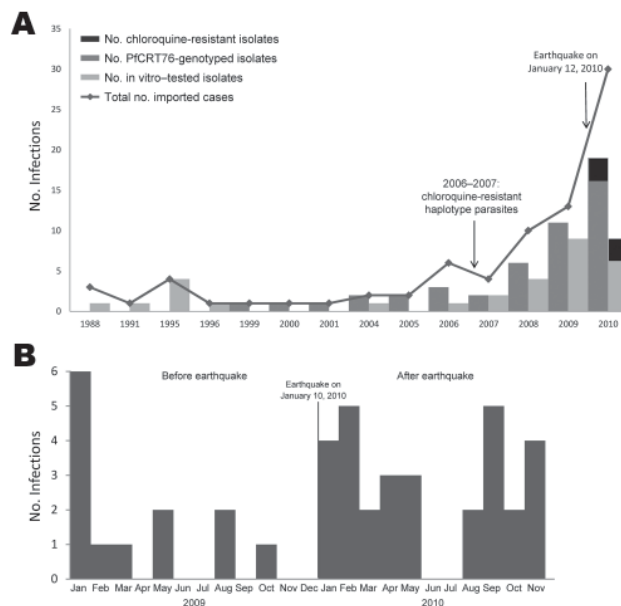


Figure 1. Surveillance during 23 years for antimalarial drug resistance in travelers returning to France and Canada from Haiti after the January 10, 2010, earthquake. A) Imported malaria cases from Haiti reported in France (1988–2010) and Canada (2007–2010). B) Total number of *Plasmodium falciparum* infections, by month, 2009 and 2010.

number of confirmed malaria cases imported from Haiti doubled during 2009–2010 (Figure 1). Approximately half of the travelers were in Haiti 2–4 weeks before the earthquake and >1 month after the earthquake. The main purpose of travel, visiting friends and relatives, decreased from 59% before to 44% after the earthquake. More than 75% of travelers did not take prophylactic medication. The proportion of severe malaria increased from 3% to 11% after January 2010 (Table 1).

Before the earthquake, all 29 isolates had the wild-type *PfcrK76* allele according to analysis by PCR–restriction fragment-length polymorphism. The mean 50% inhibitory concentration ( $IC_{50}$ ) of chloroquine for the 24 isolates tested *ex vivo* by the  $^3H$ -hypoxanthine uptake inhibition method was 27 nM (95% CI 23–31). These results are consistent with those of an unpublished study conducted in Haiti during 2007 to monitor chloroquine resistance (Jean-François Vely, unpub. data). In that study, Haiti's National Malaria Program, in collaboration with the National Malaria Reference Centre in France, found the chloroquine-sensitive genotype in 146 *P. falciparum*–positive samples in 6 departments (Artibonite, Centre, Grand'Anse, Nord, Nord-Ouest, Ouest) (Figure 2) (12). After the earthquake, 2 (11%) of 19 isolates analyzed by pyrosequencing and PCR–restriction fragment-length polymorphism showed a mixed *Pfcr76K+T* genotype. The ratios of K to T genotypes before and after *in vitro* adaptation were

0.75:0.25 and 0.23:0.77, respectively, for patient 1, and 0.58:0.42 and 0.25:0.75, respectively, for patient 2. The *Pfcr72–76* haplotype was CVMNK before adaptation and CVIET after adaptation for both patients by sequencing. Resistance was confirmed by *in vitro* methods after culture adaptation. Both isolates had high chloroquine  $IC_{50}$  (506 nM and 708 nM, respectively) and high chloroquine  $IC_{50}$  isolate:*Pf3D7* (chloroquine susceptible clone) ratio (20 and 27, respectively) (Table 2).

Patient 1, a 58-year-old woman, was in Haiti during October 2009–January 2010; she returned after the earthquake to Canada, where she sought care for malaise, fever, diarrhea, and vomiting. She reported no previous malaria and no other travel during the previous 2 years. For patient 2, a 16-year-old girl, malaria was diagnosed in Canada on February 25, 2010, after 3 days of fever. She had traveled to Haiti in the past 2 months before malaria was diagnosed and did not report any other recent travel.

## Conclusions

The number of *P. falciparum*–infected travelers returning from Haiti has increased since January 2010,

Table 1. Characteristics of travelers returning from Haiti to France, 1988–2010, and Canada, 2007–2010

Characteristic	Before earthquake, n = 49*	After earthquake, n = 30*
Median age, y (range)	44 (0.7–69)	36 (2–77)
Sex		
M	32 (68)	19 (63)
F	15 (32)	11 (37)
Country of residence		
France	49 (100)	27 (90)
Canada	0	3 (10)
<i>Plasmodium falciparum</i> infection	47 (100)	27 (100)
Chemoprophylaxis		
No	37 (76)	23 (77)
Yes	1 (2)	2 (7)
Unknown	11 (22)	5 (17)
Duration of stay		
≤2 wk	5 (17)	3 (14)
2–4 wk	14 (47)	6 (29)
1–3 mo	7 (23)	7 (33)
>3 mo	4 (13)	5 (24)
Purpose of travel		
Tourism	4 (12)	3 (13)
Visit friends and family	20 (59)	10 (44)
Business	5 (15)	3 (13)
Military	1 (3)	0
Residents or expatriates	1 (3)	5 (22)
≥6 mo		
Other	3 (9)	2 (9)
Severe malaria		
Yes	1 (3)	3 (11)
No	28 (97)	24 (89)
Median parasitemia (range)†	0.47 (0.001–12.000)	0.57 (0.04–14.00)

\*Values are no. (%) except as indicated. Numbers may not add to totals because of missing information.

†Percentage of infected erythrocytes per mL blood.



Figure 2. Departments of Haiti.

probably because of the higher number of aid workers and visitors and increased *P. falciparum* malaria transmission. Data suggest that the earthquake and ensuing hurricane and floods created the necessary conditions—inadequate shelters, population movement, and still water—to increase the incidence of malaria and possibly spread the recently identified chloroquine-resistant strains of *P. falciparum* (10). In France and Canada, laboratory surveillance for malaria found that 2 travelers from Haiti carried chloroquine-resistant strains. In vitro culture might have selected resistant strains not observed initially by ex vivo methods. After carefully interviewing these patients about their travels, we found no evidence to cause doubt that they had acquired malaria in Haiti. Alternatively, the resistant strains could have come to Haiti after the earthquake through human activity, as occurred in the cholera outbreak (13).

Table 2. Molecular genotypes and in vitro susceptibility for *Plasmodium falciparum* isolates from patients returning to France and Canada from Haiti

Characteristics	Before earthquake, n = 49	After earthquake, n = 30
In vitro analysis	n = 24	n = 10
IC <sub>50</sub> for chloroquine, nmol/L (mean 95% CI)	27 (23–31)	35 (12–105)*
No. isolates resistant†		
Yes	0	2
No	24	8
Molecular marker analysis, no. (%) isolates	n = 29	n = 19
PfCRT K76	29	17 (89.5)
PfCRT K76+76T	0	2 (10.5)
PfCRT 76T	0	0

\*The 2 resistant isolates are included with an IC<sub>50</sub> of 506 nmol/L and 708 nmol/L. IC<sub>50</sub>, 50% inhibitory concentration.

†A threshold of IC<sub>50</sub> = 100 nmol/L is applied to determine resistant isolates (consensus between the laboratories in France and Canada) and in vitro susceptibility (IC<sub>50</sub>) for the isolates from patients returning from Haiti.

The origin of the chloroquine-resistant strains identified in Haiti is uncertain. The *PfcrT* CVIET haplotype is common in Southeast Asia and sub-Saharan Africa and was found in the 2006–2007 study in Haiti (10).

Regardless of origin, containing the spread of chloroquine-resistant parasites is crucial. Malaria elimination is a goal in Haiti, and it has been strengthened after recent events, but the effects of malaria and many other factors affect the achievability of this goal (14). Control measures, possibly mirroring those used to contain artemisinin resistance in Southeast Asia, should be concentrated in Haiti to prevent resistance spreading to the rest of Hispaniola (15). However, lack of consensus on the use of molecular and in vitro data for policy change will hamper decision making. Neither the chloroquine-resistant *PfcrT*76T genotype nor the elevated chloroquine IC<sub>50</sub> perfectly predicts treatment failure because of confounding factors like acquired immunity.

Our study has several limitations. Returning travelers are not a representative sample of the Haitian population, and the sample of isolates was limited. The origin of the resistant strains is not defined. Also, the precise location of infection is not reported. Nevertheless, travelers are useful sentinels of emerging resistance in areas where little information is available, providing surveillance data in real time with standardized methods. This nonimmune population also facilitates detection of resistant isolates.

Our data highlight the need to implement a therapeutic efficacy surveillance study for assessing in vivo chloroquine sensitivity, which is essential for providing information for rational control strategies and guiding prophylaxis recommendations in Haiti. In addition, physicians treating malaria acquired in Haiti should be aware of the possibility of chloroquine-resistant infections. Patients with persistent fever despite treatment and infected travelers reporting adherence to chloroquine prophylaxis should be treated with alternate antimalarial drug therapy.

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