Epidemiological and clinical aspects of imported Malaria (***)

During the last decades enormous strides have been made towards malaria eradication; nevertheless according to the data published by WHO in 1980 [2] about 210 million persons were still affected by malaria all over the world. Thus, despite the immense efforts made in malaria eradication the worldwide prevalence of malaria has dramatically increased and malaria is still prevalent in many countries of Tropical Africa, Middle and Far East, Central and South America. The development of insecticide resistance among anopheline mosquitoes, drug resistance among Plasmodium species and socio-economic difficulties in many of the endemic countries provide evidence as to why the malaria situation causes so much concern in many parts of the world [4, 6, 36, 37, 38].

Indigenous malaria common in Europe during the 18th and 19th century decreased greatly during this century until the 1960s, when the results of the continent-wide malaria eradication programme became evident. However, all over Europe the problem of imported malaria from other parts of the world has become more serious in the last decade. In fact the persistence of large endemic areas together with a significant growth in international air travel has resulted in a steady increase of the number of imported malaria cases among those developed areas where the disease had been successfully eradicated in the past. In Italy, indigenous cases are no more reported for several years, nevertheless there has been a significant increase in the number of imported malaria cases notified in the last decade, with a peak in 1978, in the wake of greater volume of international airway travel [4, 5, 7, 8, 16, 18, 20, 29]. The growing problem of imported malaria into countries, as Italy, where the disease has been eradicated, must be regarded as a “high risk” condition for giving

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(****) Relazione presentata alla « Giornata di studio sulla Malaria » (Roma, 23 settembre 1983).
rise to indigenous foci of transmission, also in respect to some local epidemiological situations. In fact in some Italian districts, such as in Maremma, Toscana, a hyperendemic area for malaria in the past, there are still present the Anopheles labranchiae with a density ranging from 31.5 to 40.5% [11]. Moreover, besides any further epidemiological considerations the well-known difficulties in the recognition of clinical cases as well as in the treatment especially of those cases arising from drug-resistant strains of malaria underline the importance of this subject today [26, 27].

In the period 1974-1981, 176 cases of imported malaria have been notified in Lazio and, among them, we collected complete epidemiological and clinical information on 39 cases hospitalized in the Clinic of Infectious Disease, Catholic University, Rome, and in which the diagnosis has been done on the basis of the patients’ history, clinical features complained and the demonstration of the plasmodium malaria parasites in blood-film.

In tables 1 and 2 there are summarized some epidemiological aspects recorded in our 39 patients and in 176 imported malaria cases notified in Lazio, in 1974-1981 (data from Ministero della Sanità - Direzione Generale dei Servizi dell'Igiene Pubblica).

In particular, of the 176 cases of imported malaria notified in Lazio in

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**Table 1** - Occurrence of imported malaria by sex, age, circumstances of infection relative to 39 patients hospitalized in the Clinic of Infectious Diseases, Catholic University and to all cases notified in Lazio in 1974-1981.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>20 yrs.</th>
<th>20-40 yrs.</th>
<th>45 yrs.</th>
<th>Tourists</th>
<th>Business visitors</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazio</td>
<td>123</td>
<td>53</td>
<td>23</td>
<td>119</td>
<td>34</td>
<td>67</td>
<td>66</td>
<td>43</td>
</tr>
<tr>
<td>Catholic Univ.</td>
<td>31</td>
<td>8</td>
<td>2</td>
<td>21</td>
<td>16</td>
<td>18</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

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**Table 2** - Occurrence of imported malaria by site of acquisition of the infection and the species of Plasmodium relative to 39 patients hospitalized in the Clinic of Infectious Diseases, Catholic University and to all cases notified in Lazio in 1974-1981.

<table>
<thead>
<tr>
<th></th>
<th>Africa</th>
<th>E. Asia</th>
<th>S. America</th>
<th>P. falciparum</th>
<th>P. vivax</th>
<th>Double infection</th>
<th>P. malariae</th>
<th>Nc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazio</td>
<td>146</td>
<td>28</td>
<td>2</td>
<td>100</td>
<td>59</td>
<td>2</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Catholic Univ.</td>
<td>32</td>
<td>5</td>
<td>2</td>
<td>22</td>
<td>15</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
1974-1981, 123 were males, 53 females and the majority of all cases was younger than 45 years old. The disease was acquired in 146 cases in Tropical Africa, 28 in East Asia and 2 in South America. The circumstances of malaria infection were so distributed according to the various categories of patients: 67 of them were tourists, 66 business visitors, 43 religious, refugees or others. One hundred cases were due to \textit{P. falciparum}, 59 to \textit{P. vivax}, two to a double infection (\textit{P. vivax} + \textit{P. falciparum}), seven to \textit{P. malariae}, while eight were not classified (table 1 and 2).

Among our patients 31 (79\%) of them were males (medium age: 40±11 yrs.), while 8 (21\%) were females (medium age: 20±12); and the majority of all malaria patients was younger than 45. As far as the origins are concerned, 32 of them were from Italy, three from U.S.A. three from African countries and one from East Asian countries.

Thirty-two of the cases (82\%) contracted the disease in Tropical Africa, five (13\%) in East Asia, and the remaining two (5\%) in South America.

The circumstances of malaria infection were so distributed according to the various categories of patients: 18 of them (46\%) were tourists, 11 (28\%) business visitors, while 10 (26\%) were religious, refugees or others.

\textit{P. falciparum} was responsible for the disease in 22 cases (39.45\%), \textit{P. vivax} in 15 (40.54\%) while a double infection (\textit{P. vivax} and \textit{P. falciparum}) was present in two cases.

In detail, the aetiology was so distributed according to the different geographical areas. Among 32 cases who acquired the disease in Africa, 21 were due to \textit{P. falciparum}, 10 to \textit{P. vivax}, one to double infection (\textit{P. vivax} + \textit{P. falciparum}). Of the 5 cases from East Asia, one was related to \textit{P. falciparum} infection, three to \textit{P. vivax}, one to a double infection (\textit{P. vivax} + \textit{P. falciparum}). Finally, the two cases from South America were both due to \textit{P. vivax} infections.

The site of the first clinical attack was Italy in 31 patients (80\%), Africa in 4 (10\%) and East Asia in the others (10\%). By taking into consideration only the 31 patients who experienced their first clinical attack in Italy, the onset of the illness has been in 27 patients (87\%) within 20 days from their return and in four (13\%) afterwards, with a statistically significant difference between these two data (p < 0.05).

The chemoprophylaxis done by chloroquine has been carried out properly in only 3 patients, improperly, for timing and dosage, in 9, not at all in 27 patients.

It is noteworthy that chemoprophylaxis has to be carried out employing different drugs according to the different geographical areas and this for the occurrence and spread of multidrug-resistant \textit{P. falciparum} species in many parts of the world [1, 13, 15, 22, 24, 32]. For prevention of sensitive plasmodium infections, chloroquine diphosphate should be taken once weekly at a dose of 500 mg (300 mg base) for the time of exposure and for 6-8 weeks after exposure. To eliminate persistent liver forms of \textit{P. vivax} or \textit{P. ovale} a course of primaquine phosphate 26.4 mg (15 mg base) daily for 14 days may be given after
leaving the area of exposure. In areas where *P. falciparum* is resistant to chloroquine but sensitive to antifol-sulfonamide combinations a weekly dose of 25 mg pyrimethamine and 0.5 gr of long-lasting sulfonamides should be taken.

*Vivax malaria* may, however, occur under this regimen and where vivax infection is likely, weekly chloroquine may be added.

The clinical features complained of by the large majority of our patients were those usual to malaria [17], and therefore we think it is unnecessary to describe them in detail; however, some particular clinical aspects of seven patients must be pointed out.

In particular we observed four patients with cerebral malaria, coming from areas of Tropical Africa, where multiresistant strains of *P. falciparum* have never been described and with high parasitaemia. In these patients there were present hyperthermia, coma, hypotonia, absence of peripheral tendon reflexes; and in one single case high level of azotemia, proteinuria and jaundice. In all patients chloroquine was immediately given intravenously: in two cases a complete resolution of the disease was achieved while two patients died despite this treatment.

The association of malaria with other infections diseases was observed in two cases, namely, with viral hepatitis B and brucellosis.

One patient with *P. vivax* malaria immediately after a clinical attack of malaria (successfully treated by chloroquine) complained of symptoms such as weakness, anorexia, jaundice, high serum levels of transaminase (ALT > 1500 IU/ml) bilirubin (> 10 mg %) and HBsAg positivity and was therefore diagnosed as affected by acute viral hepatitis type B. This patient completely recovered from both malaria and, after a period of 60 days, hepatitis, with also the disappearance of HBsAg from blood.

One patient from Eritrea and with an anamnestic ingestion of goat's milk complained, after a clinical attack of *P. vivax* malaria, of low grade fever, weakness, sweats, generalized aches and pains and presented Brucella agglutinating antibodies (1:800) in the serum. For this reason, he was treated with, besides chloroquine for 5 days, also with tetracycline for 30 days. In this patient a complete recovery from both the diseases was obtained.

A delayed attack of *P. vivax* malaria was demonstrated in one patient 5 months after his return from Tropical Africa. It is worthy to note that in this case an improper timing and dosage, chloroquine chemoprophylaxis had been carried out.

Although most malaria infections have a well-defined incubation period of ten days to four weeks after the exposure, there are cases with a much longer natural incubation period i.e. up to 50 days for *P. falciparum* and to 13 months for *P. vivax* [6, 14, 33]. Some peculiar aspects of the exo-erythrocytic cycle may be taken into account to explain these differences [3]. In fact sporozoites differentiate into schizonts and into hypnozoite of tissue cycle, which are responsible either for the delayed attack or the relapse of *P. vivax* malaria. This differentiation seems to be influenced by climatic factors: in fact during
cold seasons a much greater number of sporozoites differentiate into hypnozoite forms, with an increased possibility of delayed primary attack [3, 33]. Indeed incubation may be also prolonged in persons taking prophylactic drugs.

At present the most important diagnostic test is the search for parasites in peripheral blood while the serological tests have less significance i.e. indirect immunofluorescence, indirect haemo-agglutination, immunodiffusion, ELISA. These tests could be employed in (1) making a retrospective diagnosis; (2) in confirming or excluding malaria as the cause of a long-standing febrile illness (3) in recognition of infection in persons returning from malarious areas; (4) in the screening for blood donors [12, 31].

All our patients were initially treated with chloroquine at the standard dosage for 5 days either orally or intravenously in the cases of cerebral malaria.

The drug of choice, in fact, for the treatment of acute attacks is chloroquine, although the emergence of chloroquine-resistant falciparum malaria in various areas of the world necessitates the use of alternative drugs in the treatment of this infection [17, 30].

The occurrence of chloroquine resistant P. falciparum strains arising in various areas of the world represents a serious setback to antimalaria programmes and implicates the usage of alternative drugs which are considerably more expensive and some are also more cumbersome to use [22, 23, 35].

Resistance of P. falciparum to chloroquine was first reported in Thailand and Colombia in 1960, and since then wide areas of Asia, Oceania, South America, East Africa have been involved [35]. There are, however, differences in the frequency and degree of chloroquine resistant falciparum in the affected areas; for example in the Indochinese Peninsula more than 90% of all P. falciparum infections are resistant.

The drug response of P. falciparum can be assessed both in vivo and in vitro. The WHO (1968) defined the various grades of the resistance according to sensitivity of malaria parasites to a standard dosage of the drug 25 mg/Kg daily for three days. Although there are difficulties in clinical observation of such patients in Tropical areas and problems in the pharmacocynetic of the drugs, nevertheless the test gave useful indications in defining the worldwide distribution and the grading of drug-resistance of P. falciparum.

A plasmodium strain is sensitive if there is a clearance of asexual parasitaemia within 7 days of treatment without recrudescence. On the contrary the resistance is defined (a) Rl if there is a clearance of asexual parasitaemia within 7 days of treatment followed by recrudescence; (b) Rr if there is a marked reduction of asexual parasitaemia but not clearance; (c) Rm if there is no marked reduction of asexual parasitaemia. Resistance to chloroquine is usually at the Rl level in South America, except for some areas of Brazil and Venezuela, while in Southeast Asia Ru-Ru resistance is much more common. In East Africa chloroquine resistant strains of P. falciparum although not so common exhibit a Rul, Rull level.

Today, a more sensitive evaluation of drug resistance is possible to be
obtained by in vitro test systems measuring reproduction and metabolic inhibition by drugs themselves [28].

Attacks of *P. falciparum* malaria resistant to chloroquine should be treated with quinine and/or the combinations of pyrimethamine with long-active sulfonamides or dapsone [17, 22, 23, 30].

However none of the currently available alternatives used alone or in combination have reached the goal of controlling the diffusion of chloroquine resistant strains of *Plasmodium falciparum*. In fact there is evidence that resistance develops relatively rapidly to the most acceptable of the alternative drugs i.e. combinations of sulfonamides and pyrimethamine and this can also be related to the indiscriminate usage of such drugs especially in the past for bacterial infections as well as for massive chemoprophylaxis programs [35].

The introduction of a wider use of new antimalarial drugs such as mefloquine and derivatives of Qinghaosu expected within a few years will be of no benefit unless other counter-measures of control are applied. These concern intensive vector control measures whether directed against the larval forms or the adults or both and an exclusive usage of the new antimalarial drugs for the treatment of acute cases and not for prophylaxis of the disease in countries or areas where the presence of chloroquine resistant forms is confirmed [25, 35].

Our experience in the management of chloroquine resistant *P. falciparum* infection concerns five patients initially treated by chloroquine who experienced a relapse of the disease within 20 days. They contracted the disease; one in east Asia and four in east Africa (Kenya, Tanzania) where chloroquine-resistant *P. falciparum* strains had been already described [13, 15, 24]. In such patients the combination of sulfonamides and pyrimethamine resulted in a complete clinical resolution without any further relapses.

Various attempts to develop different types of malaria vaccine have been made in recent years [9, 10, 19, 34]. The mechanisms of protection are basically different according to the various types of plasmodial antigens used for immunization.

The sporozoite antigens will stimulate a protective response able to inhibit the liver cell localization of malarial parasites; the merozoite antigens and the red blood cell antigens will result in the development of an effective immunity blocking the erythrocyte localization of plasmodium; while the gamete antigens will be useless in protective immunity but effective for the interruption of malaria transmission.

However, the principal goal to be achieved is not to have crude preparations but highly purified antigens. The sophisticated procedures based on the most modern techniques of molecular biology and genetic engineering [10, 34] made it possible to obtain such purified preparations which are at present under investigation.

A further prospective in the development of prophylaxis of malaria concerns the study of the red blood cell receptors for malaria parasites and in particular two different receptors for *P. falciparum* and *P. vivax* have been
identified [21]. In the future, it could be possible to chemically or immuno-
logically alter the receptor and thus block the red blood cell infection by the
merozoites.

In conclusion, today, imported malaria represents for Italy a growing medical
problem especially because an increasing number of cases are now occurring in
the wake of greater speed and volume of international travel. Therefore, malaria
must be suspected in any patient with fever of unknown or doubtful origin who
has been to a tropical area, especially but not exclusively, if the attack occurs
within 20 days from the return and this for the possible existence of delayed
attacks of malaria.

The diagnosis, suspected on the basis of the patient’s history, must always
be confirmed by the clinical observation and by microscopical examination of
the blood. As soon as a correct diagnosis of malaria has been made a specific
treatment must be instituted. In particular the choice of the antimalarial drug
must be made taking into account the geographical area where the disease has
presumably been contracted and this for the possible presence of drug-resistant
strains of plasmodia.

The clinical association of malaria with other infectious diseases, we ob-
erved in two cases, underlines the need for an accurate clinical and laboratory
investigation in every patient. In fact subjects coming from endemic malarious
areas can contract, besides malaria, other infectious diseases which could be
initially misunderstood, especially if the clinical symptoms of malaria — as it
usually happens — are predominant.
REFERENCES


