4. スタンバイ治療

1）概　説

スタンバイ治療とは、マラリアを疑わせる発熱があり、迅速に医療機関を受診できない場合に、緊急避難的に抗マラリア薬を服用する方法で、マラリアによる重症化や死亡を予防する方法と捉えることができる。

わが国では予防内服は法律的に確立した医療行為であるが、スタンバイ治療はその点不明確である。したがって、熟練していない医療従事者がスタンバイ治療を勧めることは避けるべきである。

具体的には以下の条件で行なう。

・マラリア流行地に入ってから7日以上が経過している。
・マラリアを疑わせる38℃以上の発熱がある。
・24時間以内に医療機関を受診するのが不可能である。

本法はあくまでも緊急避難的な処置であり、医療機関の受診に取って代わるものではない。また、スタンバイ治療後も可及的速やかに医療機関を受診しなければならないが、なぜならば発熱の原因がマラリア以外の可能性もあり、またマラリアであったとしても、スタンバイ治療で服用した薬剤が無効のこともありうるからである。

2）実施基準

マラリアの高リスク地域であれば予防内服が勧められるので、スタンバイ治療が勧められるのは一般に低リスク地域の場合である。しかし、マラリアの高リスク地域でも、予防薬が禁忌あるいは入手不可能、旅行者が予防内服を希望しない（あるいは拒否する）場合などでは、緊急避難的にスタンバイ治療の実施を考慮する必要がある。

しかし、本法は服薬指導において高度の厳密さが要求され、対

象者の自己責任も強く要求される予防方法である。さらにわが国で処方する場合、法律的に未解決な問題も残されている。このため、本法は一般の医療機関では実施すべきではなく、必要な場合は専門医療機関に紹介することを原則とする。

3）スタンバイ治療の問題

スタンバイ治療ではマラリアの感染・発症を抑えないこと（失敗すると、後の手段は限られる）、服用法が複雑で間違いが起きやすいこと、解熱しない場合に対応の判断が難しいことなどを理解しておく必要がある。

4）スタンバイ治療薬

わが国でスタンバイ治療の対象となる薬剤は、マラリア治療薬として認可されているものであり、メフロキン、スルファドキシン／ピリメタミン合剤（商品名ファンシダール）、キニーネ経口薬の3種類である。メフロキンの効果は高いが、精神神経系副作用が問題であり（予防での使用よりも60倍高い）、スルファドキシン／ピリメタミン合剤では耐性の問題があり、キニーネ経口薬ではコンプライアンスが不良になりがちである。

5．小児、妊婦、授乳婦への対応

1）小　児

a）概　説

マラリア流行地の住民では小児が多く罹患し、特に死亡例の殆どは小児であるとされる。Non–immuneの小児はマラリアに罹患すると、特に重症化や死亡の危険が高くなる。また、小児では使用できる抗マラリア薬に制限があること、嘔吐しやすいことなどから、治療に難渋をきたしやすい。したがって、マラリア流行地に小児を帯同するのはできるだけ避けるべきである。特にヨーロッパやアメリカでは、マラリア流行地からの移住者が流行地の親族を訪問するときに（VFRs : visiting friends and relatives）小児を帯同し、帰国後に発病する例が多くみられるが、わが国でも最近経験されるようになってきた。

b）防蚊対策

小児においては、DEETを頻回にスプレーあるいは塗布することにより、全身性の中毒反応や脳症が生じたと報告されている。しかし、DEETの使用量とそれらの副作用には著明な相関はみられず、因果関係が確認されたとは言えない場合も多い。通常の使用では重篤な副作用のリスクは極めて低いものと考えられる。ただし、小児は成人よりDEETに対する感受性が高いと考えて、10%あるいはそれ以下の製剤を使用するのが望ましく、特に眼、鼻腔、口腔に曝露を生ずるようなスプレーや塗布をしないよう注意が必要である。手にスプレーや塗布をすることも、その後に口に入る可能性があるので避けなければならない。できるだけ長袖服・長ズボンなどを着用し、それによりスプレーや塗布を最小限にする。ピレスロイド系殺虫剤に浸漬し

た蚊帳は、小児にとっても安全であるとされている。

c）予防内服

メフロキンの投与はわが国では小児を対象としていないが、欧米では5kg以上の小児に処方されている。その場合、1回量を5mg/kgとする方法や、体重5～12kgでは1/4錠、13～24kgでは1/2錠、25～35kgでは3/4錠、36kg以上では1錠とする方法がある。ドキシサイクリンの投与は一般に8歳未満の小児には禁忌であるが、国によっては12歳未満を禁忌としているところもある。クロロキン、プログアニルはすべての年齢の小児に投与が可能であるが、薬剤耐性の問題により使用価値は低下している。アトバコン／プログアニル合剤は、11kg未満の小児には推奨されない（最近米国では5kg以上に使用可能とした）。

海外ではクロロキン製剤として小児用シロップがあるが、ほとんどの抗マラリア薬は苦く、小児が嫌うことが多いので、投薬にあたり工夫が必要である。

抗マラリア薬は子供の手の届かないところに保管し、容器は子供が開けられないようにする。

2）妊　婦

a）概説

妊婦がマラリアに罹患すると、低血糖や肺水腫／ARDSを起こして重症化や死亡の危険が高くなり、また流産、早産、低体重児出産や、先天性マラリアの児の出生なども起こしやすい。従って、妊婦がマラリア流行地へ旅行することはできるだけ避けるべきである。

b）防蚊対策

妊婦は特に蚊に刺されやすいとの報告があるが、これは妊娠による生理学的変化が原因と考えられている。したがって、妊婦は夜間に短時間外出する場合でも、昆虫忌避剤の使用が望ましい。DEETを通常通りに使用した場合には、胎児に対する影響はないと考えられており、動物実験でも催奇形性は報告されていない。しかし高濃度のDEETを避け、10～30％の製剤を最小限使用することが勧められる。ピレスロイド系殺虫剤に浸漬した蚊帳も問題ないとされている。

c）予防内服

メフロキンについては、欧米では妊娠４ヶ月頃以降からの処方が行われているが、わが国では妊婦への投与は認められていない。ドキシサイクリンの投与は、全妊娠期間を通じて禁忌である。クロロキン、プログアニルは全妊娠期間を通じて安全であるとされるが、薬剤耐性の問題で使用価値は低下している。妊婦におけるアトバコン／プログアニル合剤の安全性を示すデータは少ないことから、現段階では投与は勧められない。

妊娠可能な女性の場合、メフロキンの服用終了後３ケ月間、ドキシサイクリンの服用終了後１週間は避妊することが望ましい。しかし、それらの予防内服中に妊娠が判明した場合、無条件に妊娠中絶の適応があるわけではない。

3）授乳婦

メフロキンは母乳中に少量移行するが、欧米では乳児には安全とされている。しかしわが国では、メフロキン服用中は授乳を避けることとされている。ドキシサイクリンの投与は禁忌である。クロロキン、プログアニルの母乳中への移行はわずかであり、安全と

されている。授乳婦におけるアトバコン／プログアニル合剤の安全性を示すデータは少ないことから、現段階では勧められない。母親が予防内服を行っている場合、乳児、特に早産の乳児、１ケ月未満の新生児、Ｇ６ＰＤ欠損症の乳児などでは、念のため、黄疸、溶血などの副作用について注意深く観察することが勧められる。

なお、母乳中に移行した抗マラリア薬の量では、いずれの薬剤でも乳児に対する予防効果はない。従って、そのような状況下の乳児の予防内服では、通常量の投与が必要となる。

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機　関　（特定の担当者のみの場合は括弧内氏名）	電　話
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新潟市民病院健康管理室	025－241－5151
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(4) 厚生労働省検疫所

http : //www.forth.go.jp/

世界のマラリア流行状況と推奨されている予防薬

地域	国名	区分＊	流行地域など	予防薬＊＊
アジア	Afghanistan	C	標高2,000m以下の地域（４－12月）	DOX MEF A/P
	Bangladesh	B	Dhakaはリスクなし	DOX MEF A/P
	Bhutan	C	南部インド国境の地域（Chirang, Samchi, Samdrupjongkhar, Sarpang, Shemgang）	DOX MEF A/P
	Burma(Myanmar)	B	Yangon、Mandalayはリスクなし	DOX MEF A/P　東部はDOX A/P
	Cambodia	B	Phnom PenhとTonle Sap湖周囲はリスクなし、Angkor Watはリスクあり	DOX MEF A/P　西部はDOX A/P
	East Timor	A		DOX MEF A/P
	Hong Kong	D	地方に限局	予防内服必要なし
	India	B	Delhi、Bombayもリスクあり、山岳地帯では2,000m以下の地域	DOX MEF A/P
	Indonesia	B	Java、Sumatraなどの都市や観光地を除く、Irian JayaやBorobuduは全域でリスクあり	DOX MEF A/P
	Laos	B	Vientianeはリスクなし	DOX MEF A/P
	Malaysia	C	地方、観光地や都市はリスクなし	DOX MEF A/P
	Nepal	C	Terai地区やインド国境の1,200m以下の地域、Kathmanduやヒマラヤはリスクなし	DOX MEF A/P
	North Korea	D	南部の軍事境界線周辺	予防内服必要なし
	Pakistan	B	2,000m以上の地域はリスクなし	DOX MEF A/P
	Philippines	C	Bohol、Catanduanes、Sebuを除く地方、Subic湾はリスクあり	DOX MEF A/P
	China	C	南部地域（とくに海南省、雲南省はリスクあり、これ以外も福建省、広東省、広西壮族自治区、貴州省、四川省、チベット自治区など）、北緯33度の北では７月から11月、25度から33度の間では５月から12月、25度以南では１年を通してリスクあり	DOX MEF A/P　一部CHL
	South Korea	D	北部の軍事境界線	予防内服必要なし
	Sri Lanka	B	Colombo、Kalutara、Nuwara Eliyaはリスクなし	DOX MEF A/P
	Thailand	B	観光地や都市はリスクなし、とくにカンボジア国境、ラオス国境、ミャンマー国境はリスクあり	DOX MEF A/P
	Viet Nam	B	観光地や都市はリスクなし	DOX MEF A/P
アフリカ	Angola	A		DOX MEF A/P
	Benin	A		DOX MEF A/P
	Botswana	B	北部地方（南緯21度以北）	DOX MEF A/P
	Brundi	A		DOX MEF A/P
	Burkina Faso	A		DOX MEF A/P
	Cameroon	A		DOX MEF A/P
	Cape Verde	C	Sao Tiago島はリスクあり	DOX MEF A/P
	Central African Republic	A		DOX MEF A/P
	Chad	A		DOX MEF A/P
	Comoros	A		DOX MEF A/P
	Congo	A		DOX MEF A/P
	DR Congo(Zaire)	A		DOX MEF A/P
	Côte d'Ivoire	A		DOX MEF A/P
	Djibouti	A		DOX MEF A/P
	Egypt	D	観光地や都市にはなく地方に限局	予防内服必要なし
	Equatorial Guinea	A		DOX MEF A/P
	Eritrea	B	2,200m以下全域にリスクあり、Asmaraはリスクなし	DOX MEF A/P
	Ethiopia	B	2,200m以下全域にリスクあり、Addis Ababaはリスクなし	DOX MEF A/P
	Gabon	A		DOX MEF A/P
	Gambia	A		DOX MEF A/P
	Ghana	A		DOX MEF A/P
	Guinea	A		DOX MEF A/P
	Guinea Bissau	A		DOX MEF A/P
	Kenya	B	2,500m以下全域にリスクあり、Nairobiはリスクなし	DOX MEF A/P
	Liberia	A		DOX MEF A/P
	Madagascar	A		DOX MEF A/P
	Malawi	A		DOX MEF A/P
	Mali	A		DOX MEF A/P
	Mauritania	A	北部を除く全域にリスクあり	DOX MEF A/P
	Mauritius	C	地方に限局してリスクあり	予防内服必要なし
	Mayotte	A		DOX MEF A/P
	Morocco	D	Rabat、Tangier、Casablanca等の都市にリスクはなく地方に限局	予防内服必要なし
	Mozambique	A		DOX MEF A/P
	Namibia	C	Kavango川とKunene川流域のみにリスクあり	DOX MEF A/P
	Nigeria	A		DOX MEF A/P
	Niger	A		DOX MEF A/P
	Rwanda	A		DOX MEF A/P
	Saõ Tome and Principe	A		DOX MEF A/P
	Senegal	A		DOX MEF A/P
	Sierra Leone	A		DOX MEF A/P
	Somalia	A		DOX MEF A/P

地域	国名	区分＊	流行地域など	予防薬＊＊
アフリカ	South Africa	C	北東部のMpumalanga州（Kruger公園を含む）、北部州、KwaZulu-Natal州などににリスクあり	DOX MEF A/P
	Sudan	A		DOX MEF A/P
	Swaziland	B	全ての低地にリスクあり	DOX MEF A/P
	Tanzania	A	1,800m以下の全域にリスクあり	DOX MEF A/P
	Togo	A		DOX MEF A/P
	Uganda	A		DOX MEF A/P
	Western Sahara	D	地方に限局してリスクあり	予防内服必要なし
	Zambia	A		DOX MEF A/P
	Zimbabwe	B	Harare、Bulawayoリスクなし	DOX MEF A/P
太平洋	Papua New Guinea	B	1,800m以下の全域にリスクあり	DOX MEF A/P
	Solomon Islands	A	Rennnel、Bellona南部、Temotu東部、Tikopia、Anuta、Fatutakaにリスクなし	DOX MEF A/P
	Vanuatu	A		DOX MEF A/P
中東	Iran	C	南部熱帯地域、Baluchestanなどにリスクあり	DOX MEF A/P
	Iraq	C	Sulaimania、Duhok、Erbil、Ninawa、Tamim、Basrahなどにリスクあり	CHL
	Oman	D	Musandam地方にリスクあり	予防内服必要なし
	Saudi Arabia	C	Jizan地区などの地方にリスクあり、Jeddah、Mecca、Medinaはリスクなし	DOX MEF A/P
	Syria	D	北部国境地域にリスクあり	CHL
	Turkey	D	南部、南東部にリスクあり	CHL
	Yemen	B	Sanaにリスクなし、2,000m以下の地域にリスクあり	DOX MEF A/P
カリブ	Dominican Republic	C	ハイチ国境にリスクあり	CHL
	Haiti	A	Labadee湾にリスクなし	CHL
中米	Belize	B	Belize市にリスクなし	CHL
	Costa Rica	D	Alajuela, Limon（Limon市にはない）, Guanacaste, Heredia州にリスクあり	CHL
	El Salvador	C	地方にリスクあり	CHL
	Guatemala	C	1,500m以下の地域のみリスクあり、AntiguaとAtitlan湖にリスクなし	CHL
	Honduras	C	地方にリスクあり	CHL
	Mexico	C	地方、とくに南部のChipas州、Quintana Roo州、Tabasco州などにリスクあり	CH
	Nicaragua	C	地方とManagua郊外にリスクあり	CHL
	Panama	B	Panama市、運河地帯を除いてリスクあり	DOX MEF A/P
南米	Argentina	D	ボリビア国境、パラグアイ国境にリスクあり	CHL
	Bolivia	C	高度2,500m以下、La Pazを除いてリスクあり	DOX MEF A/P
	Brazil	C	アマゾン地域（大都市でも流行あり）にリスクあり	DOX MEF A/P
	Colombia	C	600m以下の地域にリスクあり、Bogotaにリスクなし	DOX MEF A/P
	Equador	C	1,500m以下の地域にリスクあり、Quitoを含む都市、観光地にリスクなし	DOX MEF A/P
	French Guiana	C	ブラジル、スリナム国境にリスクあり	DOX MEF A/P
	Guyana	C	内陸部のみにリスクあり	DOX MEF A/P
	Paraguay	C	Alto Parana、Caaguazu、Canendiyuにリスクあり	CHL
	Peru	B	Lima、Lima南部の海岸部、高地にリスクなし	DOX MEF A/P
	Surinam	B	Paramariboを含む北緯５度以北にリスクあり	DOX MEF A/P
	Venezuela	C	地方にリスクあり	DOX MEF A/P
NIS	Armenia	D	西部国境地帯にリスクあり	予防内服必要なし
	Azerbaijan	D	Agcabdi, Bardaなどにリスクあり	予防内服必要なし
	Georgia	D	南東部に限局してリスクあり	予防内服必要なし
	Kyrgyz	D	南部、西部のタジク、ウズベク国境のみにリスクあり	予防内服必要なし
	Tajikistan	D	南部国境、中部（Dushanbe）、西部（Gorno Badakhshan）、北部地域（Leninabad）にリスクあり	予防内服必要なし
	Turkmenistan	D	Mary地方にリスクあり	予防内服必要なし
	Uzbekistan	D	Uzynskiyなどにリスクあり	予防内服必要なし

＊区分

A：全土でマラリアが流行している国。人口密集地や旅行者が訪れることが多い地域でのマラリアリスクが高い場合。
例：ガーナ、コンゴ

B：首都、あるいは大都市とその周辺に存在しないが、他の地域には存在する国。
例：ケニア、エチオピア、モーリタニア（首都を含む北部砂漠地域にはマラリアのリスクはないが人口の多い南部地域にリスクあり）、インド（全土に流行となっているがデリーを中心とした地域でのリスクは低い）

C：限局した地域にリスクがある国。
例：マレーシア、ネパール

D：マラリアの報告はあるものの非常に限局しており、旅行者が罹患する可能性がかなり低いと考えられる国。
例：グルジア、エジプト（特殊な旅行事情、例えば学術調査などで辺境などに滞在する場合には注意）

注）流行は戦争や経済状態悪化によるインフラの破壊などでも常に変化しているため、ここでの区分はあくまで参考として、実際にその地域に出かける前の確認が必要です。

＊＊予防薬

DOX：ドキシサイクリン
MEF：メフロキン
CHL：クロロキン
A/P：アトバコン／プログアニル合剤
ただしクロロキンの適用地域では、わが国の場合メフロキンで代用可能。

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CDC : Traveler's Health（http : //www.cdc.gov/travel/yb/outline.htm）
WHO : International Travel and Health（http : //www.who.int/ith/countrylist01.html）
アフリカに関してはMARA/ARMA Project（http : //www.mara.org.za/）

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Brief review

Trends in malaria cases in Japan

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Abstract

Just after World War II, more than 10,000 malaria cases per year were reported in Japan, including indigenous, imported and induced malaria. Malaria has been successfully eradicated since 1961 in Japan and now only imported malaria cases are encountered. However, as the number of Japanese people who are going abroad and also the number of foreigners who are visiting Japan increases (about 16 and 5 millions, respectively, in 2001), so does the chance for Japanese doctors to see imported malaria or transfusion-transmitted malaria cases. In fact, the total number of the patients with acute malaria in Japan has been around 100–150 annually for the last 10 years. Of those, about 75% are Japanese and 25% are foreigners, and about 75% are male and 25% are female. The peak age is in the 20 s. Recently, about 45% of patients are *Plasmodium falciparum* and another 45% *Plasmodium vivax* infections. The former species is likely to be seen in travelers coming back from African countries and the latter is mainly from Asian countries. The important issue is that patients in Japan have not been diagnosed promptly nor treated properly because doctors in Japan are no longer familiar with tropical medicine. Therefore, some patients are dying from severe malaria as a consequence. As it is, most of the effective medicines for drug-resistant malaria or severe malaria have not been registered in Japan. There is now a need for medical practitioners to focus on travel medicine in Japan.

Keywords: Imported malaria; Japan; Travel medicine

1. Introduction

In 1947 just after World War II, about 12,000 malaria cases including indigenous, imported or transfused malaria were reported according to the surveillance and statistics of the Ministry of Health and Welfare, currently the Ministry of Health, Labour and Welfare (MHLW) of Japan. Owing to the dedicated effort made through the community-based malaria control programs in local settings in Japan, indigenous malaria has been eradicated since 1961 (Ishigaki City Office, 1999). In time, the Japanese economy grew and the density of the responsible mosquitoes for the transmission such as *Anopheles sinensis* and *Anopheles minimus* decreased with the promotion of hygiene. However, the malaria situation in endemic areas, particularly in developing countries in the tropics, has not improved dramatically; in fact, it is reported to be worse partly because of the emergence of drug-resistant malaria and insecticide resistant mosquitoes. Deterioration of the current malaria situation has also been caused by global environmental

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changes and population movements. Many people now are traveling in malarious areas, visiting friends and relatives, and coming (back) to regions or countries where there is no malaria. Consequently, the spread of malaria is now a very big burden not only for people in malarious areas but also for those in non-malarious areas (Schlagenhauf, 2001). Japan is not an exception to this problem, because the number of international travelers from/to Japan is steadily increasing (16,215,647 Japanese people traveled abroad and 5,286,310 foreign citizens came to Japan in 2001). As a result, no fewer than 100 imported malaria cases have been reported annually since 1990 (Ohtomo and Takeuchi, 1998). A higher incidence of fatalities than that reported in other developed countries has also been seen in Japan, because prompt and proper diagnosis and treatment are not readily instituted by physicians. In this article, we review current trends of imported malaria cases in Japan.

2. The Research Group supported by the MHLW

2.1. The role of the Research Group

Because of the side effects of chloroquine such as retinopathy among chronic users with renal diseases, administration of the drug has been prohibited for malaria patients as well. Since then, oral quinine had been the only licensed drug for malaria for decades. In order to conquer the situation of the shortage of the available drugs in Japan for the treatment of malaria and other tropical diseases, a Research Group on the Chemotherapy of Tropical Diseases has been established since 1980 supported by a grant from the MHLW. At last in 1987, "Fansidar® (pyrimethamine/sulfadoxine)" was registered in Japan, and quite recently in October 2001, "Mephaquin® SS tablets 275 (mefloquine)" was allowed to be marketed in Japan as a result of the continuing effort of the Research Group.

The Research Group is importing other non-registered antimalarials after obtaining permission for their use as orphan drugs from the MHLW and checking their quality at the National Institute of Health Sciences to clear the Japanese Good Manufacturing Practice standards. The drugs are then distributed to 23 Research Group member hospitals or universities throughout Japan for the malaria patients have access ready to the drugs. Those antimalarials are chloroquine, primaquine, injectable quinine, artesunate (i.v.) (oral/rectal/intramusclar/intravenous), atovaquone/proguanil, and artemether/lumefantrine. The web page of the Research Group is now a useful one (http://www.ims.u-tokyo.ac.jp/didai/orphan/, at present in Japanese only).

2.2. Statistics of malaria

The Research Group analyzes demographic data together with questionnaire-based studies on imported malaria cases. Purpose of the travels, destination and period of travels, prophylactic antimalarials used, initial diagnosis made, chief complaint, present and past histories, species of the parasites infected, and laboratory data during hospitalization, have been asked and compiled. The Research Group is also collecting data on the efficacy or adverse effects of the drugs when they are used.

Table 1 shows the number of malaria cases through 1990–2000. During those 11 years, 103–132 cases were identified annually and, of them, 19–36% were foreign visitors. People coming from India have been the largest in number followed by those from the Philippines. The highest number of fatalities was observed in 1998 when the number of deaths was four (data not shown). Because of the increasing number of Japanese travelers to African countries nowadays, the proportion of falciparum malaria cases seems to be

Table 1
Number of malaria cases by year and species, reported by the Research Group, 1990–2000

Year	Species						Total[a]
	P.f.	*P.v.*	*P.o.*	*P.m.*	Mix	Unknown	
1990	40	62	3	0	5	6	116 (28)
1991	43	63	0	3	3	2	114 (41)
1992	26	70	3	0	4	9	112 (38)
1993	40	60	5	2	3	2	112 (27)
1994	46	39	4	3	5	7	104 (28)
1995	56	58	6	1	4	0	125 (30)
1996	42	49	8	1	0	3	103 (36)
1997	46	53	2	1	3	7	112 (28)
1998	51	45	2	1	2	3	104 (20)
1999	40	66	4	1	4	4	119 (28)
2000	61	56	7	1	3	4	132 (27)

[a] Figures in the parentheses are the number of foreign patients.

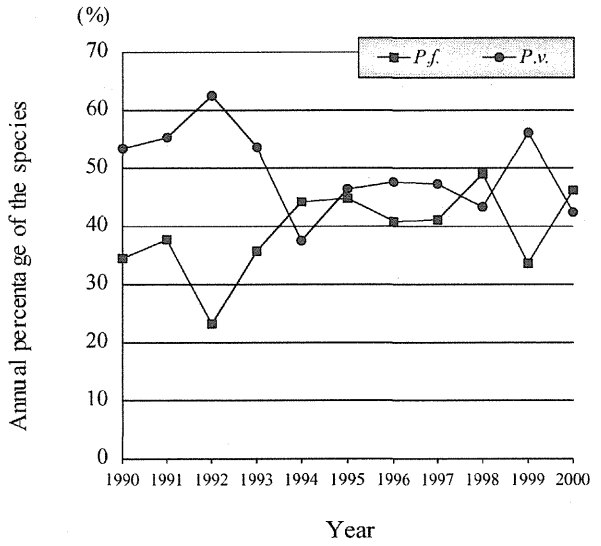

Fig. 1. Annual percentage of falciparum and vivax malaria cases, 1990–2000.

gradually increasing. This trend is illustrated in Fig. 1. From 1994, the proportion of falciparum malaria patients became comparable to that of vivax patients, and the available data on Japanese patients show that nearly three-fourth of them were suffering from falciparum malaria (data not shown).

Trends of malaria treatment have been analyzed and precisely reported by one of the present authors (Kimura et al., 2003). Briefly, mefloquine was used for treatment only in 4.4% of cases in 1990, whereas it has now become more widely used at 78% in 2000. To our surprise, artesunate was administered initially for 36% of the total number of patients in 2000.

3. Current statistics for malaria under the new law

3.1. The revised law for the control of infectious diseases

On and after 1 April 1999, a new law which is called "The law concerning the prevention of infectious diseases and medical care for patients of infectious diseases" was effective. The law before the revision was enacted in 1898 and was quite outdated after 100 years of application. In the new law, infectious diseases are categorized in five groups according to the severity and infectivity: "Group 1" consists of seven diseases namely Ebola hemorrhagic fever, Lassa fever, Crimean-Congo hemorrhagic fever, Marburg disease, Pest (Plague, Severe Acute Respiratory Syndrome (SARS) and Smallpox); "Group 2" has six diseases namely Typhoid fever, Paratyphoid fever, Diphtheria, Cholera, Bacillary dysentery (Shigellosis), Acute poliomyelitis (Polio); "Group 3" has only *Escherichia coli* diarrhea such as O157; "Group 4" is currently made up of 30 diseases including such vector-borne diseases as Malaria, Yellow fever, and West Nile fever; and "Group 5" is of 42 other diseases i.e. Amoebiasis, Syphilis, and Influenza. There is another category of "New infectious diseases" which will include emerging infectious diseases human beings have never before contracted.

Under the new law, malaria is now one of the diseases to be reported to the Governor by the physician who diagnoses a patient within 7 days. The reporting system has been simplified after the revision of the law by submitting a questionnaire in which the following questions are asked: (1) sex, (2) age, (3) how the diagnosis was made (microscopic, serologic, symptomatic, or by other instruments), (4) description of the chief complaints, (5) date of onset, (6) date of admission to hospital, (7) date of definitive diagnosis, (8) suspected date of contraction, (9) date of death (if the patient is already dead when diagnosed), (10) places of residence for the last few years, (11) suspected place of where malaria was acquired, (12) possibility of being bitten by the mosquitoes, (13) suspected route of infection, and (14) if there are friends or relatives around who are complaining of similar symptoms at the same time. Through this questionnaire, we cannot identify the patient or even know his/her citizenship. Doctors are not asked to submit slide smears of the patient to be re-checked by experts, therefore we suspect there might be some misdiagnosis in deciding the species. In fact, there were some symptomatically diagnosed malaria cases reported without our knowing whether the patients were showing parasitemia. Severity of the patient is not fully described, drugs used for the treatment are not reported, and, as it is, the outcome is not known at all. However, the number of cases reported has been increasing because, under the new law, doctors not reporting a case will be punished with a fine of no more than 300,000 Japanese yen (around 2150 €).

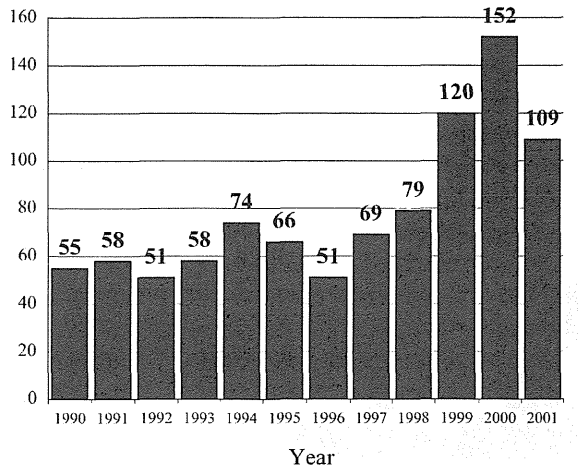

Fig. 2. Number of malaria cases by year, officially reported by MHLW, 1990–2001.

3.2. Statistics of malaria officially announced by the MHLW

The MHLW of Japan announced the annual number of malaria cases reported to the ministry (Fig. 2). It seems that the reporting system had not been working effectively under the previous law before the revision in 1999, because the number of the patients is about a half of that reported by the Research Group each year (Table 1). In the National Epidemiological Surveillance of Infectious Diseases (NESID) under the new law conducted by the National Institute of Infectious Diseases (NIID), the number of malaria cases have been officially reported (Table 2) (NIID and IDCD, 2001; NIID, 2003). The largest number of malaria patients ever reported in 2000 may be a reflection of the new regulations on reporting system. However in 2001, as the annual number of Japanese people who went abroad decreased by 1.6 million as a result of the 11 September terrorist attack in 2000, and so did the number of imported malaria patients in Japan. Now the number of cases of falciparum malaria is greater than that of vivax malaria, and the species-unknown cases are far larger than those reported by the Research Group. The ratio of males to females is about 75–25% for the last 3 years (data not shown) (NIID, 2003). Distribution of age of the patients reported in 2001 is shown in Fig. 3. The highest incidence is observed in the late 20 s, and this trend is observed every year. Young patients whose ages are in the 20 s are likely to be infected during their summer vacation through August to September (data not shown) (NIID, 2003).

Table 2
Number of malaria cases by year and species, reported in NESID, 1999–2001

Year	Species					Total
	P.f.	*P.v.*	*P.o.*	*P.m.*	Unknown	
1999[a]	41	53	3	0	13	110
2000	64	55	6	2	25	152
2001	54	39	4	1	11	109

[a] The period is from April to December.

4. Induced malaria in Japan

4.1. Reports of transfused malaria before and after World War II

The first report of transfusion-transmitted malaria in Japan was described by Sakai (1935) including two vivax malaria cases; one was a 1-year and 6-month-old boy who received 20 ml of whole blood from his father for the auxiliary treatment of bacillary dysentery, and the other was a 1-year and 1-month-old boy who received totally 60 ml of whole blood from his father for the auxiliary treatment of pertussis. Totally 28 cases of transfused malaria were reported before World War II, in which most of the blood donors were patients' parents but 6 paid blood donors were included (Takada and Nakayama, 1948). During wartime, those paid blood donors were likely to be veterans coming back from tropical pacific areas where malaria was very endemic. Of course, the possibility of transfusion-transmitted malaria was well known to medical technicians in those days, but there was no systematic way to identify the infectious blood. After the war, preserved blood was mainly used for the transfusion, which increased the chance of infection. Then, the first case of preserved blood transfusion-transmitted malaria was reported in 1955 in a 28-year-old man receiving totally 3400 ml of the blood during lung surgery (Takada, 1955). Twenty-two transfused malaria cases after World War II were summarized by Ito et al. (1985) reporting also that the total number of reported transfusion-transmitted

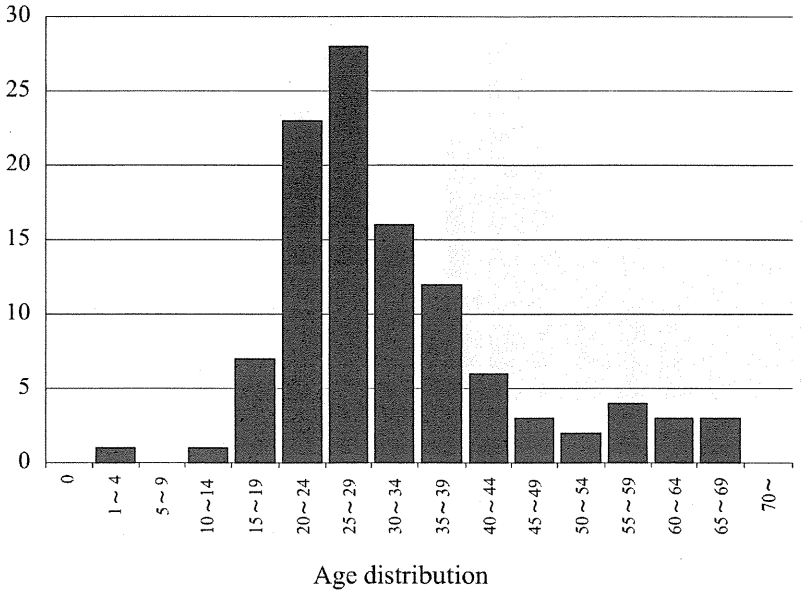

Fig. 3. Age distribution of imported malaria cases in Japan in 2001.

malaria cases in Japan was 57 (1 *Plasmodium falciparum* case, 41 *Plasmodium vivax* cases, 1 *Plasmodium ovale* case, and 14 cases from unknown species). In 1991, platelet transfusion-transmitted malaria was reported in a 70-year-old woman patient suffering from thrombocytopenia, who had been unsuccessfully treated as a consequence (Kano and Suzuki, 1994a). This case was the last case of transfusion-transmitted malaria case in Japan, and is the 75th reported transfused case so far within the authors' investigation.

4.2. Reports of other induced malaria

Malaria infection associated with needle injury or usage of contaminated syringes has also been reported in Japan since 1954. The first report was of nine cases of malaria among drug users sharing the same syringe (Otsuru and Kamo, 1954). After World War II, many people including veterans were homeless and jobless, indulging in the intoxication of drugs or narcotics, sometimes selling their own blood as an act of desperation, and consequently spreading malaria parasites. Morishita (1959) summarized the 346 syringe-associated malaria cases among these people during 1951–1957.

The first nosocomial malaria case was a 21-year-old nurse, most probably transmitted by accidental needle injury from a falciparum malaria patient whom she was taking care of at the hospital (Amano et al., 1976). Chloroquine 600 mg, sulformethoxine 1000 mg and pyrimethamine 50 mg treatment was administered through a stomach tube after she fell into coma but this could not save her life. Another needle-associated falciparum malaria case reported in 1983 was a 35-year-old male who was successfully treated and cured (Kimura et al., 2003).

No iatrogenic malaria was reported in Japan transmitted, for example, by non-sterilized surgical operation, through contaminated catheter, or by hypnozoite-infected liver transplantation. So-called laboratory malaria, which may happen among researchers who are cultivating the *P. falciparum* parasites, has never been reported in Japan, either.

5. New drugs to be introduced in Japan

5.1. Lessons learnt from halofantrine

Halofantrine has been reported to be effective since 1984 involving more than 2500 patients in 30 countries, and particularly for the treatment of multi-drug-resistant malaria in the world, because its chemical structure is quite unique and not closely related

to any other antimalarials. The first case of malaria successfully treated with halofantrine in Japan was reported in 1992, who was a 39-year-old Pakistani male suffering from *P. vivax* malaria (Yodonawa et al., 1992). Parasite clearance was rapid and fever dropped dramatically. No adverse reaction caused by the drug was reported except slight nausea. Following this case, the first author (S.K.) of the present paper and his group reported a total of 8 imported cases who were successfully treated with halofantrine: 5 *P.f.* and 2 *P.v.*; all Japanese male, 1 *P.f.* and *P.m.* mixed; foreign female (Masuda et al., 1992; Kano et al., 1993; Obana et al., 1994; Kano and Suzuki, 1994b). It was in 1994 when we first experienced recrudescence of falciparum malaria after treatment with halofantrine (Kano et al., 1994). In order to meet this resistance, we established in vitro halofantrine susceptibility test (Shikado et al., 1996).

We formed the opinion, as a result of this experience, that halofantrine was very effective, safe and tolerable for the treatment of all species of malaria. However, in 1993, a clinical study involving 400 patients on the Thai–Myanmar border revealed cardiac effects of halofantrine, including one sudden death after the treatment (Nosten et al., 1993). Then there were some spontaneous reports of serious ventricular dysrythmiasis with prolongation of QT intervals, so we attempted to monitor ECG while we were treating the patients with halofantrine. We instituted the treatment for two Japanese imported malaria cases (*P.o.*: male 22 years old and *P.v.*: male 51 years old) with informed consent, and monitored the ECGs. Consequently, we found that the QT intervals were slightly prolonged with unaffected QRS intervals. No symptoms or signs were observed on their cardiac system other than ECG findings (Kano et al., 1995; Kano, 1995). WHO announced a drug alert for halofantrine in which conditions were described which doctors should abide by (WHO, 1993). Further careful studies on individual Japanese patients to confirm its efficacy or tolerance are needed before halofantrine can be generally used in Japan.

5.2. *Artemisinin derivatives and their combination therapy*

Artemether is a chemical extract of the herb qinghao (*Artemisia annua* L.) that has been used for about 2000 years in Chinese traditional medicine for the treatment of fever and malaria. This drug has been reported to be particularly useful for the treatment of severe and complicated falciparum malaria. The first case of severe malaria treated with artemether (i.m.) in Japan was a 28-year-old Japanese male who had been traveling in Africa (Kano et al., 1988). On admission, he was already comatose with a parasitemia of 17%. Artemether (i.m.) was administered intramuscularly to the patient with the informed consent of his family. He was successfully cured with no consequent sequelae. In those days, artemisinin derivatives were only distributed by limited authorities in China, from whom the drug had been kindly given to the first author (S.K.). The second case treated with artemether (i.m.) in Japan was a much more severe case of a patient with mixed infection with falciparum and vivax malaria, who showed *P. falciparum* parasitemia at 29% (Hosaka et al., 1992). His deep coma improved soon after the administration of the drug. We did not understand why the artemisinin derivatives were so effective, but an experimental study conducted on the morphology of *P. falciparum* in an owl monkey confirmed the effect of artemether (Kawai et al., 1993).

Various regimens of the administration of artemisinin derivatives were introduced in Japan using tablet, suppository, intramuscular or intravenous fluid. About that time, we already knew that the recrudescence rate was high when one of the artemisinin derivatives, artesunate, was used as single monotherapy (Kondou et al., 1994). Anyway, artesunate or other artemisinin derivatives have not been officially registered for use in Japan, the above-mentioned Research Group have stocked Plasmotrim®-Lactab (artesunate tablet) and Plasmotrim®-Rectcaps (artesunate suppository) in case we need to treat severe and complicated malaria in Japan. Quite recently, several new data have been reported by Looareesuwan and his group in Mahidol University, Thailand, that combination therapy with artesunate (i.v.) followed by mefloquine is quite effective for the treatment of both drug-resistant malaria and severe malaria. This combination has been tried in Japan on three patients and the outcomes reported (Yasuoka et al., 2001; Itoda et al., 2002, Yoshizawa et al., 2002). Now, trends in action towards multi-drug-resistant malaria are being developed with new combination therapies that include artemisinin derivatives. Artemether-lumefantrine (Coartem®/

Riamet®) will be one of the very promising combinations (Ishizaki et al., 2003), which will be accepted for general use in Japan.

6. Conclusion

Although the number of Japanese travelers going abroad is increasing, 45% are visiting Europe and North America, 45% are traveling to Asian countries where Korea and Taiwan are the most popular, and only 2% are going to African countries. Therefore, the chances of contracting malaria will be smaller for Japanese travelers than for American or European travelers. Moreover, the number of foreign travelers coming to Japan is not high (about 5 million) as compared to France (>70 million) or United Kingdom (>20 million). Introduction of the parasites through a migrating population who may be frequently visiting friends and relatives is not a primary concern in Japan. Nevertheless, we have to be fully prepared for the continuing increase of malaria patients, particularly from areas where drug-resistant malaria is endemic.

The total amount of blood donations is around 6 million a year in Japan. Therefore, if we apply the estimate of incidence of transfusion-transmitted malaria in the United States which is about 1 or 2 in 10 million Units (Mungai et al., 2001), the possibility of parasitic contamination in preserved blood for transfusion in Japan may be nil, if we abide by the US guidelines on blood donor selection. In fact, the Japanese guidelines are stricter than in the US', so the chance of transfused malaria is very small in Japan.

A surveillance system of malaria patients in Japan has been enforced by the MHLW after the enactment of the revised infectious diseases control law in April 1999. However, the information we get from the survey has to be augmented by that obtained through the activities of the Research Group. Integration of the two independent surveillance systems should be envisaged. Another problem to be solved is the drug preservation and distribution system under the Research Group. The MHLW of Japan only allow use of Fansidar® and Mephaquin® officially, but encourages the Research Group at the same time to be fully prepared with new drug therapy for severe malaria cases. Efforts have to be made by the members of the Research Group, for example, by publishing case reports and guidelines, until MHLW accept the importance of introducing effective new drugs.

The significance of chemoprophylaxis has not been well recognized in Japan, but after the approval of mefloquine for use by MHLW not only for treatment but also for prophylaxis, physicians are encouraged to prescribe the drug for international travelers. Still, not many Japanese physicians are confident with tropical or travel medicine, and guidelines on the prevention of malaria using appropriate drugs have to be established as soon as possible. Mefloquine resistant malaria has been reported widely in Asian malarious areas, and indeed there are already some reports of its resistance in Japan. We have to prepare for use of another good chemoprophylactic regimen applying, for instance, atovaquone/proguanil, primaquine, doxycycline or minocycline (Lin et al., 2001).

In Japan, there are now some other research groups on travel medicine, on vaccine development, on drug development, and on field survey and control, which are, respectively, supported by grants from the Japanese government. Integration of the malaria research will yield fruitful results for the control of imported malaria cases in Japan.

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