INTRODUCTION

The Republic of Anophelia, despite having no physical territory, is distributed globally. Its citizens are dedicated to spreading knowledge of the history of malaria and of the scientific advances in the diagnosis and therapy of this deadly disease. The name is derived from *Anopheles*, the mosquito genus responsible for transmitting malaria among humans. Production of stamps is a tool used by the Republic's founder, Dr. Marco Corsi, to disseminate information about malaria.

Malaria is endemic in tropical and subtropical climates, but until the middle of the 20th century it was much more widely spread. It is caused by protozoan parasites of the genus Plasmodium which are transmitted by bites of infected Anopheles mosquitoes. The four primary species of Plasmodium capable of infecting humans are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. In the last century a fifth species, *P. knowlesi*, has been identified as responsible for rare cases of transmission from infected monkeys to humans.

Malaria caused by *Plasmodium falciparum* is the most common and deadly form of the disease. It is estimated to affect more than 500 million people annually and to pose a health risk to up to 2.4 billion people. It has been judged by the World Health Organization (WHO) to be the direct cause of more than 1 million deaths annually and to pose the single greatest morbidity and mortality burden in children. The risk of malaria transmission is much greater than in the past, particularly as a result of travel to and from endemic regions (WHO 2006).

One hundred and nine countries were endemic for malaria in 2008, 45 within the WHO African region (WHO 2008). While malaria is considered a rare disease in Europe, North America, Australia and Japan, it is endemic throughout the tropics. The occurrence of malaria in Europe and the USA is almost exclusively due to disease importation resulting from travel to endemic areas.

Plasmodium life cycle

The basic elements of the Plasmodium life cycle are the same for all species:

- Transmission begins when a female Anopheles mosquito feeds on a person with malaria and ingests blood containing gametocytes.
- During the following 1-2 weeks, gametocytes inside the mosquito reproduce sexually and develop into infective sporozoites.
- When the mosquito feeds, sporozoites are inoculated into human blood and quickly infect hepatocytes.
- Schizogony occurs within infected hepatocytes rupture after 1-2 weeks, releasing merozoites.
- Merozoites then invade red blood cells (RBCs), where they transform into trophozoites.
- Young trophozoites grow and develop into schizonts, which then rupture the RBC, releasing merozoites into the plasma.
- These merozoites then rapidly invade new RBCs.

- Repeated cycles of schizogony are responsible for the clinical symptoms.
- A small percentage of parasites become gametocytes which undergo sexual reproduction when taken up by a mosquito.
- Gametocytes then develop into infective sporozoites within the mosquito, thereby continuing the transmission cycle.

Each Plasmodium species has a specific incubation period. This is usually 10-20 days for *P. vivax* and *P. ovale*, 7-14 days for *P. falciparum*, and about 1 month for *P. malariae*. In temperate climates, however, some strains of *P. vivax* may not cause clinical illness until a year after infection due to the presence of a hypnozoite form, which can survive in human hepatocytes for several months before emerging. The pre-erythrocytic part of the malarial life cycle can be bypassed when infection is transmitted by blood transfusions, organ transplants, or sharing of contaminated needles, or by horizontal transmission from an infected mother to an unborn foetus.

Treatment of malaria

Historically, malaria was treated by drug monotherapy, most notably with quinine and chloroquine. Quinine is still effective, but it is rarely used for the treatment of uncomplicated malaria because of the length of the treatment and the side effects. Chloroquine has been the standard treatment for more than 50 years. Unfortunately, drug resistance developed and is now highly prevalent in nearly all endemic regions. Resistance has been reported to most anti-malarial drugs except for Arteminisin-based Combination Therapy (ACT). Current antimalarial therapy simultaneously employs two or more blood schizontocidal drugs with independent modes of action. This improves therapeutic efficacy and also delays the development of resistance to the individual components of the combination.

To combat the development of resistance, WHO has recommended that monotherapy be eliminated and that malaria should be treated with a combination of an artemisinin derivative and another anti-malarial with a different mechanism of action and long-lasting presence in the human body. This combination is referred to as ACT. Artemisinin derivatives rapidly decrease the parasite biomass, while the presence of a second anti-malarial with a different mechanism of action reduces the probability of the emergence of resistant strains.