There has been a steady rise in attention on malaria, and the political will to eradicate this disease. About half the world’s population lives at risk of malaria infection, in about 100 countries. The world has woken up to the fact that malaria remains a persistent and recurrent scourge to hundreds of millions of people each year. The rapidity with which this change has occurred is quite astounding and, if continued, brings promise for the counterventions aim to target the various life cycle stages, as the parasite transforms from an infectious sporozoite, to a thriving parasite in hepatocytes, followed by red blood cells and back to an Anopheles mosquito vector.

Plasmodium – the causative agent of malaria

Malaria has often been synonymous with the most deadly species, *P. falciparum*, which has received the vast majority of research and development support. While present in many parts of the world, *P. falciparum* is most prevalent in Sub Saharan Africa, causing upwards of 90% of all malaria illness and death on the African continent. *Plasmodium vivax*, on the other hand, is most widespread, particularly from a global perspective looking outside Africa, and current publications are bringing awareness to the fact that *P. vivax* causes severe illness and potentially death, in addition to morbidity and socioeconomic problems [2]. *Plasmodium knowlesi*, originally known as a parasite of macaque monkeys in South East Asia, has also become a concern, since hundreds (and perhaps thousands) of clinical cases of *P. knowlesi* malaria have been diagnosed in Malaysia and surrounding countries, with a number of reported deaths [3].

*Plasmodium* is a eukaryotic parasite with multiple life-cycle stages requiring the timely regulation and expression of 5,000 to 6,000 genes [5]. The disease is propagated each time a female anopheline mosquito injects infective sporozoites while taking a blood meal. If even one sporozoite successfully traverses the skin and blood vessels and manages to gain access to and grow in liver cells, the disease has the chance to progress. Sporozoites invade and develop in hepatocytes forming multinucleated schizonts, carrying tens of thousands of merozoite progeny. When released into the blood stream (6-15 days later, depending on the species) the cyclical process of

<table>
<thead>
<tr>
<th>Species</th>
<th>Dormant liver forms</th>
<th>Target cells</th>
<th>Length of erythrocytic cycle</th>
<th>Forms in peripheral blood smear</th>
<th>Microscopy: Giemsa-stained asexual features*</th>
<th>Average number of merozoites released</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em></td>
<td>-</td>
<td>All erythrocytes</td>
<td>48h</td>
<td>R, G</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td><em>P. vivax</em></td>
<td>+</td>
<td>Reticulocytes</td>
<td>48h</td>
<td>R, T, S, G</td>
<td>Schüffner’s dots, ameboid</td>
<td>16</td>
</tr>
<tr>
<td><em>P. ovale</em></td>
<td>+</td>
<td>Reticulocytes</td>
<td>48h</td>
<td>R, T, S, G</td>
<td>Schüffner’s dots, ameboid</td>
<td>8</td>
</tr>
<tr>
<td><em>P. malariae</em></td>
<td>-</td>
<td>Older erythrocytes</td>
<td>72h</td>
<td>R, T, S, G</td>
<td>Band forms</td>
<td>8</td>
</tr>
<tr>
<td><em>P. knowlesi</em></td>
<td>-</td>
<td>All erythrocytes</td>
<td>24h</td>
<td>R, T, S, G</td>
<td>Band forms possible</td>
<td>12</td>
</tr>
</tbody>
</table>

R= Ring; T= Trophozoite; S= Schizont; G= Gametocyte
*distinguishing features of infected asexual stage forms*

**Table 1. Comparison of Plasmodium species infecting humans.**
In addition to primary liver-stage schizonts, \textit{P. vivax} and \textit{P. ovale} produce dormant liver forms, called hypnozoites, which can relapse and initiate repeated erythrocytic cycles of infection as soon as two weeks, or years after an initial blood-stage infection and treatment. The molecular makeup and biology of hypnozoites remain unknown. Knowing what triggers their activation could lead to new clinical tests to detect the presence of these forms, and guide treatment.

**Diagnoses**

Effective, rapid and timely diagnosis of malaria is of utmost importance. Clinical symptoms appear when the parasite destroys red blood cells during the erythrocytic cycle; symptoms include fever, chills and malaise that initially can be confused with other infections. It is critical that when healthcare personnel suspect malaria infection a clinical history is taken, including travel to malaria endemic areas, and that light microscopy analysis of a blood film stained with Giemsa is performed, the gold standard for malaria diagnosis. Documentation of the species or multiple species is important for determining the proper treatment.

Few laboratories are equipped to process blood samples and run polymerase chain reaction (PCR) tests to confirm the \textit{Plasmodium} species in specimens. However, Rapid Diagnostic Tests (RDTs) – the craze of the past decade, and wave of the future – are commercially available kits that detect \textit{Plasmodium} species-specific antigens. Recently, RDTs have been positioned in malaria-endemic regions to “fill the gap” of effective, reliable and timely diagnosis. Yet, implementation in the field has had to overcome challenges related to quality assurance, and interpretation of results \cite{7, 8}. According to the Centers for Disease Control and Prevention, Binax NOW is the only RDT approved for use in the United States; it detects the histidine rich protein II (HRPII) from \textit{P. falciparum} and another antigen present in all five species (\textit{Pf}, \textit{Pv}, \textit{Pm}, \textit{Po}, \textit{Pk}). Yet, definitive diagnosis should be confirmed by standard microscopy.

**Treatments**

Currently primaquine is the only drug available that eliminates the dormant hypnozoites, and it faces resistance and contraindications. Alternatives are urgently needed and more emphasis on \textit{P. vivax} research is likely to lead to such discoveries \cite{2, 9}. Drug development research has brought about new options to treat blood-stage infections, with Artemisinin Combination Therapies (ACTs) taking centre stage since 2004. But recent examples of artemisinin resistance emphasise the need for intense surveillance...
Complete treatment of the blood-stage parasites is important to ward off the development of drug resistance, and the possible recrudescence of blood-stage parasitaemia and illness.

Vaccine development

Vaccines have been in the pipeline for 30 years, and yet the potential is at an all-time high to make them a reality - someday. Gone are the days of optimistically predicting a malaria vaccine will be available within five years or so, but the potential within a matter of decades is considered a reality by many today. Current vaccine candidates have been based on one or a few proteins discovered 10, 20 or more years ago [11]. While there have been signs of protective effects in clinical trials, up to about 50%, it is clear that an all-encompassing malaria vaccine is still not within reach. The ideal vaccine would provide complete protection against infection and disease for all species. Current vaccines being tested are predominantly to protect against *P. falciparum*.

Genomic and post-genomic advances

Malaria genome sequences have been completed for *P. falciparum*, *P. vivax* and *P. knowlesi*, and additional laboratory strains and patient isolates are being sequenced from around the world for comparative purposes [5]. Sequence data are providing the means for understanding the parasite’s “omics”: genome, transcriptome, proteome, metabolome, etc. High throughput omics technologies also enable global understandings; e.g. of the mechanisms of parasite variation and drug resistance. Investigations have advanced from a one-gene, one-protein at a time approach to the large-scale potential of comparative studies and systems biology approaches to help develop vaccines, drugs or diagnostics [Figure 2]. With this comes the recognition of the intricacies of each species and host-parasite interactions. Systems biology approaches can lead to the identification of host and parasite factors, or biomarkers, that are associated with the various clinical presentations seen in patients with malaria. Human or non-human primate clinical samples, obtained in experimental settings, can be studied to generate mathematical models, and incorporate computational biology predictions into the iterative design of experimental plans to better understand the disease state, and pinpoint novel targets for clinical testing and interventions.

Education

With today’s capability for widespread communications and expansion of educational tools comes the responsibility of propagating accurate knowledge. Malaria education can expand, and become as widespread as cell phones, evident in the far reaches of villages around the world. Twenty years ago the Malaria Foundation International was founded with the belief that ‘no one would want to be left out’ of the process of fighting malaria and making it history. We have seen incremental developments in this direction, and social networking is a tool unforeseen in those days that makes it possible for the broadest participation. If malaria education of young children, especially in malaria-stricken countries, is emphasised today, knowledge would become widespread, and the push for eradication would benefit from a constant boost of new supporters.

Malaria is preventable and treatable, but current tools are inadequate to eradicate this disease. Continued research and development for diagnostics, new drugs and vaccines are necessary in parallel with epidemiological and clinical surveillance programmes to break the cycle of transmission, illness and death. The current post-genomics era brings hope for currently unpredictable solutions, particularly with regards to systems biology approaches, which may enable the identification of host or parasite factors that can become clinical indicators for future laboratory tests.

References


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