

# Antimalarial patent landscape: a qualitative and quantitative analysis

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*The present study attempts to capture the development in the technology sphere of antimalarial agents through patent landscaping. The study addresses patents describing novel technologies related to some of the new and promising antimalarial drug targets. It also attempts to cover the patent landscape of the existing antimalarial drugs and vaccines. Lastly, a quantitative patent analysis of global antimalarial agents has been presented to arrive at an evidence-based policy-making in order to eradicate malaria.*

**Keywords:** Antimalarial drug resistance, antimalarial drug targets, antimalarial vaccines, patent landscape, *Plasmodium*.

MALARIA is a major global health problem. It is the leading cause of death in children, and directly and adversely affects economic development<sup>1</sup>. The World Health Organization (WHO) places 3.3 billion people of the world at risk of contracting malaria, with 2.1 billion at low risk and 1.2 billion at high risk<sup>2,3</sup>. Vaccination, vector control and parasitocidal drugs are the three main strategies which are presently being used to control the disease. Currently parasitocidal drugs are the main line of disease control until vaccination or mosquito control can be implemented more successfully<sup>4</sup>. For decades, malaria chemotherapy has relied on a limited number of drugs. However, the acquisition and spread of drug resistance has led to increase in morbidity and mortality rates in many malaria endemic regions. Increasing burden caused by drug-resistant parasites has stimulated scientist and researchers to look for novel drug targets and inhibitors<sup>5</sup>. For these reasons it is imperative that new lines of drugs should be explored before existing drugs lose too much efficacy<sup>6</sup>.

Currently, malaria drug development is research priority. Vaccine development is one aspect of the efforts to control malaria, but an effective vaccine should transform prospects of reducing this disease. Malaria vaccines can be the cornerstone of malaria eradication<sup>7</sup>. Worldwide funding for malaria vaccines has increased recently from US\$ 50 million to around US\$ 60–70 million, but remains an order of magnitude below that for HIV vaccine development<sup>8</sup>. Exciting progress made over the past decade has revived scientific attention and has attracted public and private funding to pursue vaccine-based intervention strategies<sup>9</sup>.

An attempt has been made in this study to present an overview of the new line of drugs that are being currently explored, through patent landscaping. A detailed description of a few novel and promising technologies (according to the authors) is also presented. Additionally, we have also made an attempt to summarize the patent landscape of the existing antimalarial drugs. A detailed overview of the current patent landscape of the malaria vaccines is also included. Lastly, to summarize the trend of global patenting activity in the field of malaria, a quantitative analysis of the global antimalarial agents has been presented.

## Methodology

The databases searched included subscription-based database Derwent Innovation Index for the period 1966–2011. The search methodology for obtaining patent publications related to the area of malaria was mainly based on keyword searches. The search strings used to collect the data are provided in the supplementary material (Tables 1–4 [available online](#)). In addition, various search strategies based on applicant, owner or assignee and country-wise coverage queries were also used.

## Patent landscape of new antimalarial drug targets

### *Cell cycle as drug targets*

Cyclin-dependent kinases (CDK) play an important role in cell cycle progression and are conserved in all eukaryotic species<sup>10</sup>. CDKs are attractive drug targets in numerous diseases and efforts have led to the identification of novel CDK-selective inhibitors in the development of treatments for infectious diseases like malaria.

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CDK has become the focus of rational drug design programmes for the development of new antimalarial agents. An initial search with the string 'cdk inhibitor' retrieved 241 patent publications claiming composition or formulation related to CDK inhibitors. One-third of the retrieved patent publications were disclosing compositions and formulation related to antineoplastic agents. A manual check of the retrieved data revealed that only 13 patent publications have described technology, related to CDK inhibition, to treat malaria.

Three CDKs have been identified in the *Plasmodium* genome<sup>11</sup>, Pfmrk, PK5 and PK6. The use of quinazolinone compounds, such as febrifugine derivatives, as inhibitors of recombinant plasmodial cyclin-dependent kinase (Pfmrk) for the treatment of protozoan infections was described in WO2004000319. Chalcones, another compound claimed as a potent inhibitor of Pfmrk, was disclosed in WO9317671.

WO200296888, granted in 2004 and assigned to Bayer Pharma AG, came out as the most dominant patent with 64 citations. The patent claimed a novel pyrimidine derivative as a potent CDK inhibitor. It was further claimed that the compound is effective at nanomolar concentrations and has much stronger CDK inhibiting activity than known agents such as olomoucine, roscovitine and kenpaullone, and can be used for treating *Plasmodium* infection. Cyclacel Limited came out as the top assignee with 10 publications related to *Plasmodium* CDK inhibitors. The most dominant patent (US2007/0021419-A1) in the Cyclacel CDK inhibitor patent portfolio describes a compound which can be used for treating antifungal and antiparasitic disorders, particularly malaria. It was further claimed that the compound is a potent protein kinase inhibitor and may also inhibit formation of the nuclear envelop, exit from the quiescent phase of the cell cycle, G1 progression, chromosome decondensation, nuclear envelope breakdown, START initiation of DNA replication, etc.

It is well established that active pharmaceutical agents can be often given in combination in order to optimize the treatment regime. We recorded 8 patent publications which described the use of a pharmaceutical combination of CDK inhibitor and another pharmaceutical agent, e.g. ErbB inhibitor (US2010/0143380), histone deacetylase inhibitor (EP1951307), vascular endothelial growth factor receptor inhibitor (EP1568368), cytosine analogue (US7772207), DNA topoisomerase-I inhibitor (US2006/0148828), gemcitabine (US2005/0267066), docetaxel (US2005/0277656), mitoxantrone (US2005/0261260), anthracycline (US2005/0222054) and 5-fluorouracil (US2005/0164976).

#### *Metabolic pathways in the apicoplast as drug targets*

The identification of apicoplast in *P. falciparum* provided new targets for drug therapy<sup>12</sup>. The apicoplast contains

metabolic pathways and housekeeping processes that differ from those of the host, thereby presenting ideal strategies for drug therapy. Compounds targeting these pathways are antimalarial and have favourable profiles based on extensive knowledge from their use as antibacterial<sup>13</sup>.

**DNA replication:** The genome of the *Plasmodium* plastid is circular and a bacterial-type DNA gyrase is required for replication of the apicoplast genome<sup>14,15</sup>. Ciprofloxacin has been shown to inhibit apicoplast DNA replication but not nuclear replication in *P. falciparum*. Recent studies validate these findings, that DNA replication is a viable therapeutic target in the apicoplast and point towards ciprofloxacin as a potential antimalarial<sup>16</sup>.

A new class of terpyridine platinum complexes, claimed to be potent intercalators of DNA and to have anti-parasitic activity was disclosed in WO9727202. Similarly, WO2003059881 disclosed a new oligopeptide compound useful for treating diseases which depend on DNA replication. Not a single patent claiming the inhibition of apicoplast DNA replication, for treating malaria was recorded.

**Transcription:** The first step in gene expression, transcription of the information in the DNA genome into messenger RNA, is carried out by RNA polymerases (RNAPs). These enzymes have become attractive targets in the development of antibiotics<sup>17</sup>. For instance, the frontline antitubercular drugs, rifampin and rifampicin, effectively inhibit bacterial RNAPs. A number of other potent inhibitors that affect different stages of transcription or target different regions of the bacterial RNAP have been reported, such as streptolydigin, microcin and myxopyronin. These proteins are attractive targets in the search for new antimalarial antibiotics.

We recorded about 20 patent publications, which described technologies for the preparation of compositions or pharmaceutical formulations, containing several antibiotics, which include transcription-inhibiting compounds like rifampin and rifampicin, for the treatment of bacterial and viral, including parasitic diseases like malaria. US2011028385 disclosed a compound for treating bacterial, viral and fungal, including parasitic diseases like malaria and the mode of action of the compound involved RNA transcription inhibition. The compound comprising an immunomodulator, that must be combined or associated with at least one substance specifically targetted against the pathogens that infected the host. Selected from chemical groups and species such as bacterial nucleic acid synthesis inhibitors (rifampicin, quinolones), and substances with antibacterial, antiparasitic, antifungal and antiviral properties, where a combination of substances can be used in the treatment of infections caused by intracellular microorganisms. A preparation containing active substances 3-*N*-formyl-hydroxylaminopropyl phosphonic

acid derivative combined with other pharmaceutical active agents like rifampin (a nucleic acid synthesis inhibitor) is described in US2004235784. It was further claimed that the pharmaceutical preparation can be used in the therapeutic and prophylactic treatment of bacterial and parasitic infections, especially malaria.

**Fatty acid synthesis:** It is one of the most attractive targets for malaria drug discovery. This pathway has been found to be the target of several classes of antimicrobial compounds, some of which have antimalarial activity<sup>18</sup>. Among the enzymes of the FASII pathway in *P. falciparum*, *FabI* or enoyl-acyl carrier protein (ACP) reductase, catalysing the final step in the chain elongation cycle, has been studied in great detail from the viewpoint of identifying potent inhibitors. Based on the potential of compounds to inhibit the bacterial enoyl-ACP reductase, inhibitory effects of triclosan, diazaborine, isoniazid and ethionamide on the *Plasmodium* enzyme and growth in culture have been studied<sup>19</sup>.

A total of seven patent publications were recorded which disclosed technology related to fatty acid synthesis (FAS) inhibition. The National Institute of Immunology (NII) and Indian Institute of Science (IISc) with three patent publications, WO200100138-A2, US2008051445-A1 and US2008161247-A1, came out as the top assignee. WO200100138-A2 described the use of hydroxydiphenyl ether class of chemicals, e.g. triclosan to inhibit the elongation in FAS in malaria parasite. US2008051445-A1 discloses a method for treating infectious diseases, such as malaria using enoyl-ACP reductase inhibitor, i.e. an inhibitor of the rate-limiting enzyme of type-II FAS pathway that pulls the cycles of fatty acid elongation to completion, in microorganisms, including malarial parasites, and which is different from the FAS I pathway in humans. Thus, it provides a treatment method that acts on a component of FAS pathway essential for growth; and exhibits potent antimalarial, antibacterial and biocidal activity. US2008161247-A1 claimed a synergistic composition for enhancing the effect of an inhibitor in inhibiting nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate (NAD<sup>+</sup>/NADP<sup>+</sup>) or reduced form of NAD<sup>+</sup>/reduced form of NADP<sup>+</sup> (NADH/NADPH)-dependent enzymes and enoyl-ACP reductase for treating malaria. The inhibitor for NAD<sup>+</sup>/NADP<sup>+</sup>-dependent enzymes and enoyl-ACP reductase is triclosan.

A compound which inhibits the growth of liver stage *Plasmodium* parasites and prevents malaria in a vertebrate subject was disclosed in WO2008147826-A1. The inhibitor of apicoplast FAS is a type-II FAS pathway inhibitor. WO2009101345-A1, assigned to Seattle Biomedical Research Centre, claimed a novel substituted bicyclic compound useful as an anti-infective medicament for the treatment and/or prevention of human/animal infections related to a pathogen with enoyl-ACP reductase enzyme or a structurally related enzyme. The compound acts as

an enoyl-ACP reductase inhibitor. US2005142204 described the technology involved in manufacturing an oral anti-malaria dosage form, comprising triclosan emulsion and/or an oil solution.

**Isoprenoid biosynthesis:** The presence of a mevalonate-independent pathway for isoprenoid biosynthesis in *P. falciparum* has been discovered. 1-Deoxy-D-xylulose-5-phosphate (DOXP) reducto isomerase plays an essential role in the non-mevalonate pathway, which is absent in humans<sup>20</sup>.

A search with the string 'DOXP malaria' retrieved seven patent publications, claiming novel compounds for treating malaria by inhibition of DOXP reducto isomerase. Among these, four patents (WO200278714, US2003144249, WO200160829, WO200041473-A2) were assigned to Jomaa Pharmaka GMBH, two patents (WO2005048715, WO2005016942) to Bioagency AG and one patent (US6638957) jointly assigned to Jomaa Pharmaka GMBH and Bioagency AG.

#### Cytosolic targets

**Folate pathway:** The folate pathway has been a major drug target. The combination of pyrimethamine, inhibiting the dihydrofolate reductase (DHFR) and sulfadoxine, inhibiting dihydropteroate synthase (DHPS), are providing to be an effective and cheap antimalarial. A method to treat severe/multi-drug resistant cerebral malaria comprising antimalarial agents  $\alpha$ ,  $\beta$ -arteether, sulfadoxin and pyrimethamine is described in US2006141024. DE4009941 claimed the use of pteridines in combination with dhfr inhibitors (pyrimethamine) and dhps inhibitors (sulfadoxine) for the treatment of malaria. We have recorded a total of 44 publications claiming the use of dhfr-inhibiting compounds. Six patent publications claimed the use of *P. falciparum* DHFR (PfDHFR) inhibiting compound as the primary drug for treating malaria. A few of the disclosed PfDHFR inhibitors are new triazine derivatives (WO2011018742-A1), new 2,4-diamine pyrimidine (WO2009048957), new pyrimidine and quinazoline derivatives (WO2004082613), new 2,4-diamino-5-phenylpyrimidine derivatives (US2004180913) and new 2,4-diaminopyrimidine (WO2003043979).

There has also been an effort to make methotrexate and aminopterin, potent inhibitors of dhfr, *in situ* from non-toxic precursors, in view of their toxicity to the host. We recorded 20 patent publications which claimed the use of methotrexate in combination with several other chemical compounds for the treatment of malaria. In the case of aminopterin we recorded only two patents mentioning the use of the drug in methods for preparing monoclonal antibody against malaria parasites.

**Glycolysis:** *Plasmodium* derives most of its energy through glycolysis, hence inhibitors of this pathway have

been studied for antimalarial activity. One of the well-studied targets is *P. falciparum* lactate dehydrogenase (PfLDH). We recorded a single patent application which (WO2011054525) claimed the use of compounds (substituted 5-membered heterocyclic) that inhibit lactate dehydrogenase (LDH) for treating malaria. It further claimed to provide compounds that are selective inhibitors of the LDH-A subunit of LDH enzymes. A large effort is focused on developing PfLDH inhibitors such as gossypol derivatives and naphthoic acid-based compounds. Not a single patent claiming the use of gossypol or naphthoic acid-based compound as a PfLDH inhibitor was recorded. But we did record four patents mentioning the use of gossypol in combination with several other chemical compounds for treating malaria.

**Salvage pathway:** *P. falciparum* purine nucleoside phosphorylase (PfPNP) is an enzyme of the salvage pathway which has been studied as potential drug targets<sup>21</sup>. WO2009082247 discloses compounds comprising PNP and purine phosphoribosyl transferase (PPRT) inhibitors which are useful for treating protozoan parasites, e.g. malaria. 5'-Methylthio-imucillin-H has been developed as a potent and selective inhibitor of PfPNP based on the crystal structure of the inhibitor-bound compound. US7098334 discloses the usage of 5'-methylthio-imucillin as 5'-methylthioadenosine phosphorylase (MTAP) inhibitor and 5'-methylthioadenosine nucleosidase (MTAN) inhibitor.

Hypoxanthine-guanine-xanthine phosphoribosyl transferase (PfHGXPRT) is another potential drug target from the salvage pathway<sup>22</sup>. PfHGXPRT catalyses the transfer of phosphoribosyl group to hypoxanthine, xanthine or guanine to give the corresponding nucleotide. US2005123557 discloses an immunotherapeutic composition comprising the HGXPRT protein or one or more isolated proteins each comprising at least one immunogenic fragment, or an isolated nucleic acid encoding the protein, and a carrier, diluent or excipient. The patent further claimed that the composition can be used to treat protozoal diseases like malaria. CN1900274 provides the recombinant protein (HGXPRT) of malignant malarial parasite hypoxanthine-guanine-xanthine ribose phosphate transferase. It was claimed that the recombinant protein HGXPRT has excellent immunogenicity and excellent enzymic kinetic characteristic, and can induce effective malarial parasite antagonizing immune response in the immunized individual and produce efficient enzymological activity.

**Redox system:** It is still a matter of debate whether compounds directed at *P. falciparum* antioxidant defence could be a valid chemotherapeutic approach<sup>23</sup>. However, it is generally accepted that oxidative stress is an important mechanism for destruction of malaria and other intracellular parasites<sup>24,25</sup>. To prevent oxidative stress, the

parasite has its own battery of defence tactics and produces its own antioxidant enzymes. The malaria parasite contains three antioxidant enzymes: superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase. Functional thioredoxin and glutathione systems have been shown to participate in antioxidant defence in *P. falciparum* and both are considered as attractive targets. The antioxidant defence of the parasite could therefore be a potential target for antimalarial chemotherapeutics. We did not record any patent claiming compounds or drug combinations which target the parasitic redox system.

**Shikimate pathway:** The discovery of the Shikimate pathway in the malaria parasite has shown the path for the discovery of new drug targets. Absence of the Shikimate pathway in mammals presents an excellent target for the development of new chemotherapeutic agents<sup>26</sup>. US6699654 claimed a composition that interferes with the growth or survival of an apicomplexan parasite by inhibiting enzymes involved in metabolic pathways of the parasite. The patent further claimed that the compound inhibits (i) the synthesis of chorismate from phosphoenolpyruvate and erythrose 4 phosphate by the Shikimate pathway, (ii) synthesis of tetrahydrofolate from chorismate by the Shikimate pathway, (iii) synthesis of ubiquinone from chorismate by the Shikimate pathway, (iv) synthesis of aromatic amino acids (phenylalanine, tyrosine and tryptophan) from chorismate by the Shikimate pathway and (v) synthesis of the menaquinone, enterobactin and vitamins E and K1 from chorismate by the Shikimate pathway.

**Mitochondrial targets:** There are two main functions of mitochondria: electron transport and protein synthesis. These appear to be essential for survival and constitute potential targets for antimalarial chemotherapy. WO2010142741, assigned to the GlaxoSmithKline (GSK) group, discloses new phenylpyridylpyridone compounds useful in the treatment of malaria caused by infection with *P. falciparum*. It was further claimed that the compound acts by inhibiting ubiquinol-cytochrome bc1 (cytbc1) oxidoreductase, inhibits electron transport and collapses mitochondrial membrane potential, which is required for a number of parasite biochemical processes.

Orotidine decarboxylase catalysing the conversion of orotidine monophosphate to uridine monophosphate has also been studied as a unique drug target and novel pyrimidine derivatives are also under consideration.

**Food vacuoles:** Haemoglobin is broken down into heme and is converted to hemozoin in the food vacuole. This pathway has been targeted by the currently available aminoquinolones<sup>27</sup>. Falcipains and plasmepsin proteases which break down haemoglobin are now considered as potential drug targets for new antimalarial agents. We recorded seven patents which claimed novel compounds

to treat malaria by inhibiting plasmepsin protease. The claimed plasmepsin inhibiting novel compounds are macrocyclic heterocyclic compound (US2010063121), substituted piperazine compounds (US2009105251), new pyrido (2,3-d)pyrimidine compounds (US2010137310), 7-aryl-3,9-diazabicyclo(3.3.1)non-6-ene derivatives (US-7427613), allophenylnorstatine-based compound (US-2005037953) and hydroxyamino acid amide derivatives (US5872262).

## Patent landscape of the existing antimalarial agents

### Drugs

**Artemisinins:** These are one of the most important classes of antimalarials for reasons that include pharmacokinetic properties, pharmacodynamic properties and activity against multi-drug resistant parasites<sup>28</sup>. We recorded a total of 203 patents claiming the use of artemisinins and their derivatives (artemether, artesunate and dihydroartemisinin) to treat malaria. The Council of Scientific and Industrial Research (CSIR)-India with 13 patent publications was the main applicant. Analysis of artemisinin-related patenting activity by country revealed that the US was by far the most prolific innovator country. After manual refining of the retrieved data, we recorded 81 patent publications which claimed new artemisinin derivatives or artemisinins as the primary drug, whereas the remaining patent publications claimed the use of artemisinins as a secondary drug in combination with several other pharmaceutical agents for the treatment of malaria.

The demand for artemisinin derived from plants may soon exceed the supply. A number of semi-synthetic routes to prepare artemisinin analogues, such as artemether and artesunate with changes to the  $\delta$ -lactone portion have been developed with the goal of improving the pharmacokinetic properties<sup>29</sup>. An approach to meet the demands for artemisinin-based therapies is to develop a totally synthetic artemisinin analogue that can be manufactured at a price competitive with that of the agricultural process. US6486199 awarded to Medicine of Malaria Venture discloses such a compound. The patent claimed of a method for treating malaria, schistosomiasis, and cancer using a spiro or dispiro 1,2,4-trioxolane. The compound was developed by Vennerstrom *et al.*<sup>30</sup> as a potent antimalarial. The compound lacks chiral centres and is synthesized in a short and economical fashion by Griesbaum co-ozonolysis involving the joining of *O*-methyl adamantanone oxime with a substituted cyclohexanone in the presence of ozone followed by post-ozonolysis side-chain elaboration. US2009042821 assigned to Ranbaxy claimed of a compound comprising spiro or dispiro 1,2,4-trioxolane antimalarials, or their pharmaceutically acceptable salts, prodrugs and ana-

logues, and processes for their preparation. Another patent assigned to Ranbaxy (US20090306091) discloses antimalarial therapy using a synthetic artemisinin derivative and bisquinoline derivative.

Similarly, US7667017 discloses another bioengineering method invented by Kielsing *et al.*<sup>31</sup>, who have transplanted plant biosynthetic genes into yeast to allow production of the artemisinin precursor artemisinic acid in yields that appear suitable for large-scale fermentation. The patent claimed of a method synthesizing isopentenyl pyrophosphate (IPP) in a host microorganism. The method includes introduction of heterologous nucleic acid sequences into the host microorganism. It was further claimed that each nucleic acid sequence codes for a different enzyme in the mevalonate pathway for producing IPP. WO2010109472 discloses a method for microbial bioconversion of arteannuin B to artemisinins.

**Lumefantrine:** A total of 41 patent publications claiming the use of lumefantrine as an antimalarial drug have been recorded. Ten patent publications claim the use of lumefantrine as the primary drug. WO2006117616 assigned to Ranbaxy claimed of a new polymorphic form of lumefantrine useful for treating or preventing malaria. IN200901437, IN200802503, IN200801677 and IN200700012 claimed of new process for the preparation of lumefantrine.

Coartem (US5677331) is a combination of artemisinin-derivatives artemether and lumefantrine and is the first fixed dose artemisinin-based combination therapy to meet WHO pre-qualification criteria for efficacy, safety and quality.

**Amodiaquine:** This belongs to the 4-aminoquinoline chemical class. It is used in combination with artesunate. We recorded 62 patent publications claiming the use of amodiaquine in combination with artesunate. Eighteen patent publications claimed the use of amodiaquine as the primary drug. Searete LLC and CSIR-India were the major applicants. ASAQ, a pharmaceutical combination of artesunate and amodiaquine, is one of the currently available antimalarial medications. The drug was devised by Drug for Neglected Disease initiative (DNDi) in partnership with Sanofi-Aventis. ASAQ is patent-free.

**Piperaquine:** A total of 18 patent publications claiming the use of piperaquine for treating malaria have been recorded. Thirteen patent publications claim the use of piperaquine as the primary drug. The mode of action of piperaquine is based upon heme binding, with an antimalarial activity against both *P. falciparum* and *P. vivax*. Piperaquine has been combined with dihydroartemisinin (CN1237416, CN101199489, CN101984970, CN101129377) with a view to provide a cheap, well-tolerated, short-course treatment regime with a high cure rate against drug-resistant parasite.

Duocotecxin and artekin are two commercially available medications of piperquine and dihydroartemisinin combination. Eurartesim is another piperquine and dihydroartemisinin combination which has been recently approved by the European Commission for the treatment of uncomplicated malaria.

*Pyronaridine:* Twenty-five patent publications claiming the use of pyronaridine as an antimalarial agent has been recorded. Seven patent publications claimed the use of pyronaridine as the primary drug. KR975895 discloses a method for preparing pyronaridine. The method is claimed to produce pyronaridine with high yield and high purity and with improved antimalarial activity. WO2006049391 (Pyramax) assigned to Shin Poong Pharmaceuticals disclosed a pharmaceutical formulation comprising artesunate and pyronaridine, which can be administered orally and is effective against resistant strains of malaria.

*Mefloquine:* We recorded 123 patent publications claiming the use of mefloquine as an antimalarial drug. Only nine patent publications were recorded which claimed the use of mefloquine as the primary drug, whereas the remaining claimed the usage of mefloquine as a secondary drug in combination with several other antimalarial compounds. EP2233481 claimed of a novel method for producing mefloquine. The method comprises of diastereoselective hydrogenation of dehydromefloquine in an inert solvent and using novel metal catalysts. US2007078161 assigned to Arakis Limited claimed new crystalline forms of (+)- and (-)-erythro mefloquine hydrochloride, useful for treating malaria. WO9821323-A2 claimed of a new synthetic oligonucleotide, which is complementary to the *P. falciparum* multi drug resistance gene and useful for restoring sensitivity to antimalarial drugs such as mefloquine.

*Quinine/quinidine:* Quinine was the first effective drug use in the treatment of malaria caused by *P. falciparum*, appearing in therapeutics in the 17th century. It remained the antimalarial drug of choice until the 1940s, when other drugs replaced it<sup>32</sup>. A search for patents claiming the use of quinine as a antimalarial drug retrieved 153 patent publications. In the last ten years only 22 patent publications were recorded which claim the use of quinine as the primary drug. WO200146188 claimed of new stereoisomerically purified forms of the compounds, quinine and quinidine and a method for determining the therapeutic profile of a compound by comparing the effects of the compound on the first and second ion channels and gastrointestinal tissue samples. US2008039492 claimed a method of optimizing the safe use of quinine and providing information that quinine affects the activity of a cytochrome p450 isozyme. US2009163540 claimed a new solid state form of quinine sulfate.

*Atovaquone:* A total of 61 patent publications claiming the use of atovaquone for treating malaria have been recorded. Six patent publications claimed the use of atovaquone as the primary antimalarial drug. WO2010001379 claimed of a new process for preparing atovaquone. The process provides higher yields of pure atovaquone, using reagents which are inexpensive while avoiding the use of heavy metals. WO2010009492 claimed of a new method for preparing atovaquone and its salt. WO2011021230 claimed of a new atovaquone–proguanil complex. Atovaquone is available as a combination preparation with proguanil that has been commercially available from GSK since 2000 as malarone for the treatment and prevention of malaria.

*Chloroquine:* This is a 4-aminoquinoline drug used in the treatment or prevention of malaria. It was until recently the most widely used antimalarial. Two hundred and seventy-three patent publications claiming the use of chloroquine have been recorded. Of these, 188 were issued or published in the last 10 years. But the emergence of drug-resistant parasitic strains is rapidly decreasing its effectiveness; however, it is still the first-line drug of choice in most sub-Saharan African countries. We recorded a total of 78 patent publications claiming the use of new compounds against chloroquine-resistant malaria. Forty-four of these were published or issued in the last 10 years. The Hoffmann La Roche & Co and the University of Namibia were the top applicants with 8 and 7 patent publications respectively. Hoffmann La Roche & Co portfolio consisted of publications claiming new or known compounds. University of Namibia patent portfolio was mainly composed of publications claiming the synthesis of metal complexes for treating chloroquine-resistant malaria.

*Pyrimethamine:* This is a medication used for treating protozoal infection, mainly malarial infection. It interferes with tetrahydrofolic acid synthesis from folic acid by inhibiting the enzyme DHFR. It is for intermittent preventive treatment, combined with sulfadoxine. One hundred and ten publications claiming the use of pyrimethamine have been recorded. Fifty-eight publications claimed the use of pyrimethamine in combination with sulfadoxine. We also observed that majority of the publications claimed the use of pyrimethamine–sulfadoxine as secondary drugs in combination with several other antimalarial agents.

Resistance to pyrimethamine is widespread. Mutations in the malarial gene for DHFR may reduce the effectiveness of pyrimethamine. In this context we recorded nine publications which disclose new compounds for treating pyrimethamine-resistant malaria.

*Primaquine:* A member of the 8-aminoquinoline group, primaquine is a medication used for the treatment of

malaria. We recorded a total of 95 patent publications claiming the use of primaquine as a primary or secondary antimalarial drug. Thirteen patents claimed the use of primaquine as the primary or major antimalarial drug. CSIR-India with six patents was the main applicant. US7183291, EP1055427 and WO200191535 from the CSIR-India portfolio claimed of new primaquine derivatives for treating malaria.

### Vaccines

*Pre-erythrocytic vaccines:* Currently, pre-erythrocytic stage (sporozoite and liver-stage) vaccines are the best supported financially, perhaps because there is a potential market in the more developed countries<sup>33</sup>. The ideal vaccine of this stage would induce high titres of functional antibodies against sporozoite to prevent all parasites entering the liver stage, and induce potent cytotoxic T-lymphocytes immunogenicity against the liver stage to kill infected hepatocytes, while not harming the human host. WO9310152 describes a vaccine derived from the circumsporozoite (CS) protein of *P. falciparum*. And it seems that there has been some progress made towards the vaccination against *P. falciparum* using the approach described therein. To date the most advanced malaria vaccine in the clinic is based on a lipoprotein particle referred to as RTS,S (WO200403718 and WO2004037189 assigned to GSK). It is a pre-erythrocytic stage particle against *P. falciparum*, which inhibits the parasite entry into liver cells. This particle contains a portion of the CS protein of *P. falciparum* fused in frame via a linear linker to the N-terminal of the S-antigen from hepatitis B. The linker may comprise a portion of preS2 from the S-antigen.

A hybrid *P. vivax* CS protein is described in WO2006088597; the publications claimed that the synthetic nucleotide fragment encoding a PvCS-hybrid protein is useful as a diagnostic reagent, for antibody production, and as a protective vaccine against infection with any strain of *P. vivax*. The methods can be used for diagnosing, preventing or treating malaria infection. A fusion protein composed of the hybrid protein of WO2006088597 and S-antigen of hepatitis B and lipoprotein particles comprising the same are described in EP2007057301. A lipoprotein particle comprising the fusion protein of EP2007057301, RTS and optionally S units is described in EP2007057296.

ICC-1132 (WO200213765) is another pre-erythrocytic candidate vaccine. It is a hepatitis B core particle, genetically engineered to include a region of the CS for high titre antibody induction. The ME-TRAP vaccine (WO2008122811) is entirely different from the other pre-erythrocytic malaria vaccines. It is a DNA vaccine that uses the prime boost approach for immunization. It uses a malaria DNA sequence known as ME (multipurpose epi-

tope) – TRAP (thombospondin-related protein). An antigen-based vaccine against malaria comprising a fusion protein derived from *P. falciparum* glutamate-rich protein (GLURP) genetically coupled to at least one other *P. falciparum* derived protein or a homologue of the fusion protein or comprising a recombinant BCG expressing the nucleic acid is described in WO2004043488.

WO2011138251 describes a lentiviral vector particle comprising in its genome at least one recombinant polynucleotide encoding at least one polypeptide(s) carrying epitope(s) of a pre-erythrocytic stage antigen of a *Plasmodium* parasite capable of infecting a mammalian host and useful for treating malaria. US6066623, US6268160, WO2006023593, WO2007027860 and WO2010062859 also claimed new compounds to be used as pre-erythrocytic vaccines.

*Anti-cytoadhesion and placental malaria vaccine:* The PfEMP-1 antigen, the main ligand for cytoadhesion of *P. falciparum*, is also being researched as a vaccine candidate. A bivalent vaccine described in WO2011061848, is comprised of proteins, one of which is chosen from the *P. falciparum* erythrocyte membrane proteins (PfEMP). WO2009080715, WO2008039390 and WO200212292 are some of the other patent publications claiming the use of PfEMP antigen.

VAR2CSA, a PfEMP variant is thought to mediate sequestration specifically to the placenta. High VAR2CSA-specific antibody titres correlate with a reduced risk of malaria-induced low birth weight. The central role of VAR2CSA in adhesion to the major ligand of placental syncytiotrophoblasts is highlighted by the loss of cytoadhesive capacity in mutant parasites that contain targeted deletion of the corresponding gene. These findings together make placental cytoadhesion a leading target for antibody-mediated vaccine strategies. WO2004067559 discloses a VAR2CSA polypeptide comprising a sequence of 3056 amino acids. It was further claimed that the polypeptide or nucleotide sequence is useful for manufacturing a composition that prophylactically or therapeutically reduces the incidence, prevalence or severity of pregnancy-associated malaria in a female subject. US77-45580 discloses a VAR2CSA sequence for the use in vaccine against pregnancy-associated malaria (PAM).

*Blood-stage vaccines:* The blood-stage vaccines are directed against the merozoite surface protein (MSP) and apical membrane protein (AMP). A vaccine that could prevent invasion of red blood cells by merozoites would prevent malaria disease<sup>34</sup>. Merozoite surface protein is the most well-characterized antigen involved in invasion, and is the basis for several candidate vaccines. US7488489, US2009214635 and US2010291095 described a hybrid protein comprising the peptide and an exogenous polypeptide sequence of MSP-3. The hybrid protein is claimed to be a good blood-stage vaccine candidate.

Another blood-stage vaccine candidate is GLURP (WO2004043488). It is an antigen-based vaccine against malaria comprising a fusion protein derived from *P. falciparum* GLURP, genetically coupled to at least one other *P. falciparum*-derived protein or a homologue of the fusion protein or comprising a recombinant BCG expressing the nucleic acid. Both GLURP and MSP-3 blood-stage candidate vaccines have been clinically assessed in Europe. WO2005040203 disclosed novel MSP-3-like family genes located on chromosome 10 of *P. falciparum*, which encode proteins useful for preparing vaccine compositions against malaria. An anti-invasion vaccine based on MSP-1 known as falciparum malaria protein-1 (FMP-1) is being clinically assessed (WO200258727, WO2003004525, WO2003084472).

The *P. falciparum* glycosyl phosphatidyl inositol (GPI) is another lead candidate for antimalarial vaccines. The glycoproteins are often attached to the cell surface via a GPI-anchor assembly. GPI-anchored proteins are ubiquitous throughout the animal kingdom and play an important role in orchestration of host-pathogen interactions during the infective process. WO200015254 describes a method of eliciting or inducing, in a mammal, an immune response by administering a composition containing a compound that induces a response to the inositol glycans domain of a GPI, but not to the lipid domain of GPI. A recombinant polypeptide showing enhanced immunogenicity, comprising a GPI structure was claimed in WO9634105. WO200024406 describes a method for treatment of mammalian diseases by activation of T-cells using GPI. WO200113923 claimed of a method which involves administration of GPI-inhibiting compounds for treating malaria. Similarly, a method for identifying inhibitors of GPI is described in WO200200919. WO2004005532 discloses a method for the preparation of glycosyl phosphatidyl inositol glycans, useful for the treatment of malaria. An heterocyclic antimalarial agent which can inhibit GPI by inhibiting the activity of the GWT1 gene product of *Plasmodium* is disclosed in WO2006016548. WO2009102717, WO2004048567 and WO2004011026 are some of the other publications claiming the use of GPI for treating malaria.

*Sexual stage vaccine:* There is little commercial funding for sexual stage vaccine candidates, since they have no market in developed countries. But sexual stage vaccine could contribute to malaria control if linked with other interventions. The US National Institute of Allergy and Infectious Diseases Malaria Vaccine Development Unit plans clinical assessment of a *P. falciparum* gametocyte candidate vaccine, Pfs25, a recombinant protein. The US Department of Health and Human Services has the strongest patent portfolio concerned with sexual stage vaccines. WO9219758 was the earliest patent recorded; claiming the use of Pfs25. WO9814472, US2003049278 and US5853739 disclosed immunogenic compositions

comprising Pfs28 fusion proteins. An immunogenic conjugate comprising at least one *Plasmodium* sexual stage surface protein (Pfs25) covalently linked to at least one *Plasmodium* CS protein, where the conjugate elicits an immune response to the sexual stage surface protein and the CS protein in a subject is described in WO2010040000.

#### *Adjuvants for malaria vaccines*

Till date vaccination has been the most cost-effective health intervention for a range of infectious diseases, and one day this will include malaria. Vaccines for malaria will require adjuvant to induce protective immune responses. Successful vaccine development requires knowing which adjuvants to use and also how to formulate adjuvants and antigens to achieve stable, safe and immunogenic vaccines. Adjuvants and delivery systems which have been approved for clinical trial testing or are components of licensed vaccines, and have been used in malaria vaccines include aluminium salts (alum), MF59<sup>TM</sup> and MPL<sup>TM</sup> (ref. 35).

Aluminium-based adjuvants, including aluminium hydroxide, aluminium phosphate and a combination of the two have been evaluated by numerous groups. The use of alum-based adjuvants for vaccines appears attractive since there are only minimal intellectual property barriers. However, the variable response, as well as formulation and characterization challenges suggest that other adjuvants should be considered.

MP59<sup>TM</sup> (US6299884 and US6451325) is an adjuvant produced by Novartis (Chiron) comprising squalene, sorbitan trioleate and Tween 80, and is approved for use in many European countries. MP59<sup>TM</sup> has also been tested in candidate vaccines against malaria. MP59 is proprietary and its use in vaccines produced by others would require a license. The original patent on MF59 emulsions (EP0399843) has been revoked in the European Patent Office. However, it may still be valid in other parts of the world. Whereas the owners of the technology have publicly indicated that in the event of a pandemic they would permit their adjuvants to be used by others, pre-negotiated licenses and supply agreements need to be established<sup>36</sup>.

MPL<sup>TM</sup> (EP0971739, EP1194166 and US6491919), patented by Croxix Corporation, is a nontoxic derivative of LPS from *Salmonella minnesota* and is a potent stimulator of T<sub>H</sub>1 response. The patents claimed an attenuated form of the lipid-A component of bacterial lipopolysaccharide (LPS). LPS and lipid-A are potent immunostimulators but have deleterious side effects, such as pyrogenicity (fever). The modifications described in Corixa's patents abate the side effects but do not disable the immunostimulatory effects of lipid-A. France patent FR2824279 (Montanides) describes water-in-oil emulsions containing squalene and mannide-monooleate as an

emulsifier and known as Montanides have been extensively used in malaria, HIV and cancer vaccine clinical trials.

Quil A (US6352697) is a saponin preparation based on defined compositions of purified saponin fractions derived from the bark of *Quillaja saponaria* Molina. The saponin preparations are useful in immunostimulating complex (iscom) matrices. The saponin preparations and iscom matrices prepared using them have particular activity as adjuvants. QS-21 is a purified component of Quil A that demonstrates low toxicity and maximum adjuvant activity. Patents that claim QS-21 are US5057540 (expired in 2008), US5583112, EP0362279 (expired in 2008) and EP0606317. AS02 (EP1126876B1 and US7357936) and AS04 (EP0671948, EP0761231 and US5750110) are proprietary adjuvants of GSK. AS02 contains MPL™ and QS-21 in an oil-in-water emulsion. AS02 is used in a malaria vaccine of GSK. AS04 also is composed of MPL, but in combination with alum. This adjuvant is used in GSK's HSV and HPV vaccine.

US2011282061 discloses adjuvant molecules that comprise of an imidazoquinoline molecule covalently linked to a phospho- or phosphonolipid group. The compounds of the invention have been shown to be inducers of interferon- $\alpha$ , IL-12 and other immunostimulatory cytokines and possess an improved activity profile in comparison to known cytokine inducers when used as adjuvants for vaccine antigens.

### Quantitative patent analysis of global antimalarial agents

#### Geographical distribution of patent publications

Figure 1 demonstrates the worldwide distribution of antimalarial patent publications which show the interest of the assignees and inventors in a particular geographical location for protecting their technology to lead in market. The highest number of patents were published through Patent Cooperation Treaty also termed as WIPO publications (PCT/WO) followed by USA (US) and Europe (EP) with 1975, 1677 and 1529 patent publications respectively. Australia (AU) leads Japan (JP) in patent publications followed by China (CN) and Germany (DE). India (IN) placed at the eighth position in patent publications showed its position in technological and research advances in antimalarials.

#### Patent publication distribution based on assignee

Figure 2 depicts the prominent players in the market of antimalaria agents. The top-10 assignees are comparatively shown, in which GSK emerges as the top applicant with 101 patents followed by CSIR-India with 56 patents and US Health (the United States of America as represented by the Secretary Department of Health and Human

Services) with 55 patents. India is a high malaria burden country and delivers good efforts in research and development through CSIR.

#### Patent publication based on top technologies area

Figure 3 represents the segregation of antimalarial patents on the basis of the International Patent Classification (IPC). A61P-033/06 (therapeutic activity of antimalarials), A61P-033/00 (antiparasitic agents), A61K-039/015 (plasmodium antigens), A61K-000/00 (preparation for medical purposes), A61P-035/00 (antineoplastic agents), C07K-014/445 (peptides from plasmodium), A61P-031/00 (anti infectives i.e. antibiotics, antiseptics, chemotherapeutics, etc.), A61K-039/002 (protozoa antigens), A61K-039/00 (medicinal preparations containing antigens or antibodies), C07H-021/04 (compounds having deoxyribosyl as saccharide radical), A61P-043/00 (drugs for specific purposes), C07K-014/435 (peptides from animals and humans), A61P-033/02 (antiprotozoals), C12N-015/30 (genes encoding protozoal proteins) and C12N-015/09 (recombinant DNA-technology) are the IPC classes which cover majority of the antimalarial patents.

#### Patent publication distribution based on inventor

Figure 4 shows the contribution of the top-10 inventors, with the top inventor being Joseph D. Cohen, who marked a significant milestone in research and development of diagnosis and treatment methods of malaria. Joseph has the highest number of patent publications (24) followed by S. Hoffman (19), Pierre Druilhe (18), S. K. Puri (16) and S. Singh (15).

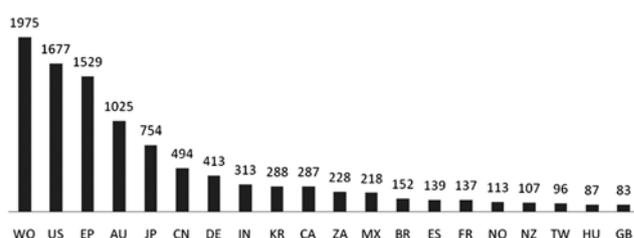


Figure 1. Country-wise distribution of antimalarial patent publications.

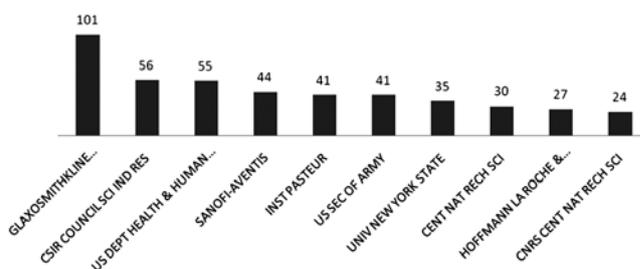


Figure 2. Assignee-wise distribution of antimalarial patent publications.

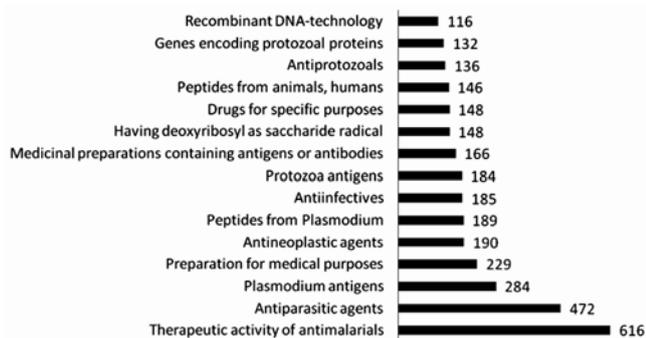


Figure 3. Technology-wise distribution of patent publications.

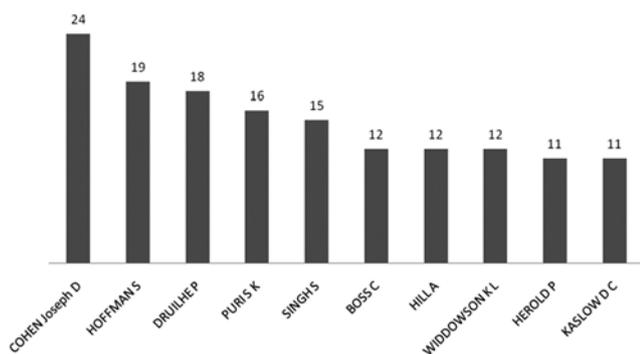


Figure 4. Inventor-wise distribution of patent publication.

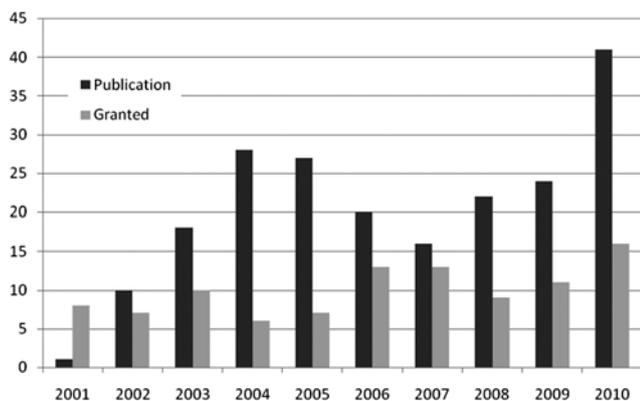


Figure 5. Trends of patent filed in United States Patent & Trademark Office.

### Summary of the antimalarial patent landscape

Malaria control has so far relied largely on a comparatively small number of chemically related drugs belonging to four classes of compounds, four aminoquinoline (chloroquine, quinine, mefloquine, amodiaquine) or eight aminoquinoline (primaquine), artemisinins and derivatives (artemisinin, artesunate, artemether, artemether, dihydroartemisinin), the antifolate compounds (pyrimethamine) and most recently naphthoquinone (atovaquone)<sup>37</sup>. We recorded a total of 1164 patents claiming the use of the four aforementioned compounds. The exist-

ing antimalarial drug patents cover half of the patented technologies against malaria. Six hundred and seventy-two patent publications claiming new compounds were recorded. Three hundred and eight-seven patent publications describing new antimalarial compounds were filed between 2005 and 2011. In case of malaria vaccine a rise in patenting activity can be seen, especially in the last 5 years. From 1961 to 1999, a total of 276 patent publications were recorded, while from 2000 to 2004, 103 patent publications and from 2005 to 2011, 227 publications were recorded.

Already a substantial number of patents have been granted within this field (Figures 5 and 6). A large number has been filed since 2001. The technical content of the antimalarial patent landscape is complex. New antimalarial compounds and their methods of preparation, combination therapies of existing pharmaceutical agents and pre-erythrocytic vaccines showed the most intense patenting activity. If grant rate follows these trends, there will soon be a significant mass of patent claims through which commercial products have to navigate through to reach the market.

The United States clearly dominates most aspects of antimalarial research, invention and patenting. This may be because most of the assignees/applicants and/or inventors are located in USA. The top public sector organizations by patent assignee are all in USA. Europe seems to be closing the gap with USA. The top two assignees Pasteur Institute and GSK are located in Europe. Ownership of antimalarial patents seems to be quite fragmented across multiple organizations. A majority of the key patented technologies which are currently undergoing development or technologies which show promise of being commercially applicable are assigned or owned by more than one organization. Majority of the drugs currently under clinical trial are sponsored or developed in collaboration with more than one organization. Under such conditions of fragmentation, the task of coordinating access to complex technologies could involve an intense and costly process.

Patenting activity in antimalarial elements has increased. In spite of having patented products and a good provision of compulsory licensing of these patented products, successful commercial applications in this field are subtle. So what are the reasons behind this – whether the money needed to conduct research is scarce, that has hampered research in developing new drugs or is there unavailability of background data pertaining to clinical trial phases, as clinical trial research is costly, lengthy and pertaining to high risk?

### Drug resistance

Drug resistance is a recurring theme in the history of infectious disease control. From a public health perspective,

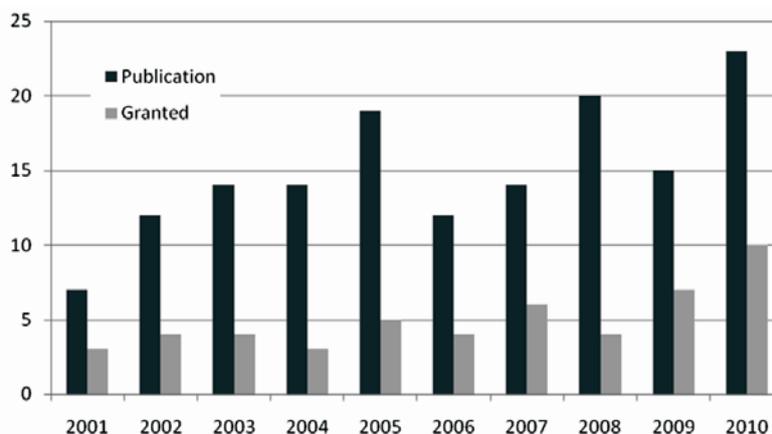


Figure 6. Trends of patent filed in European Patent Office.

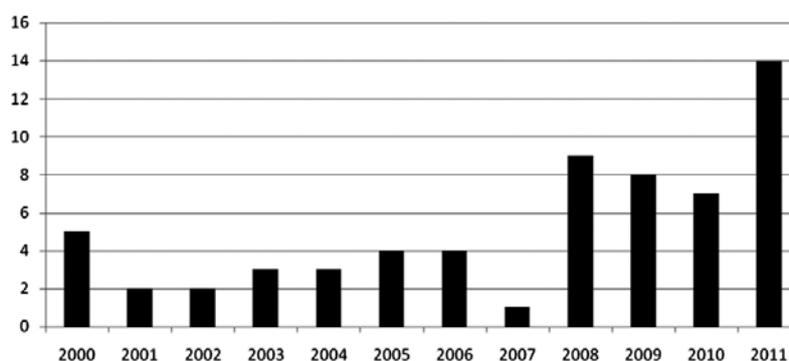


Figure 7. Trends of patent publications disclosing compounds against drug-resistant malaria.

drug resistance is a critical factor that undermines malaria control. The clinical consequences of such resistance are well described in terms of increased morbidity and mortality<sup>38,39</sup>. A search for patents disclosing technologies to treat drug-resistant malaria and manual refining of the retrieved data resulted in 230 publications. Hoffman la Roche and CSIR with 7 and 6 patent publications respectively in their portfolio were the top applicants. The Hoffman la Roche portfolio consisted of publications disclosing compounds – piperidine derivatives (WO991-2532), beta-alkoxy-acrylate derivatives (WO9902150), aralkyl quinolin-4-yl-diamine derivatives (WO9718193), bis-quinoline diamine derivatives (WO9535288), amino-quinoline derivatives (US5596002) and dithiane derivatives (US5302727) against chloroquine-resistant and chloroquine-sensitive pathogens.

Poor-quality antimalarial drug is another menace which is threatening to jeopardize the progress and investment in combating malaria. Nayyar *et al.*<sup>40</sup> point out that around 36% of antimalarial drugs analysed in Southeast Asia were fake, whereas a third of the samples in sub-Saharan Africa failed chemical testing for containing too much or too little of the active ingredient, potentially encouraging drug resistance. Antimalarial drug resistance

poses a real threat to the impact of most of the malaria control programmes. Figure 7 shows trends of patent publications disclosing compounds against drug-resistant malaria. Intensive monitoring of drug resistance along with the strategies to reduce its future emergence and spread is needed.

### Marketing challenges

The antimalarial market is one of the biggest markets with around half a billion treatments needed per year, but majority of the patients are located in low-income countries and are unable to pay for their treatment. Norrby *et al.*<sup>41</sup> have suggested that the main reason why the pharmaceutical industry has been unwilling to invest in antibiotic research development is because of the poor returns on investment owing to increasing cost of drug development, caused, in part, by increasing demands from regulatory authorities and stricter pricing controls imposed by governments. They further suggest that another problem for the industry is that if it is able to achieve a high sales figure, the result is likely to be more rapid emergence of resistance which would have an effect on future sales.

The major cost in developing new drugs arises during the clinical development programme, especially during the phase-II and phase-III clinical trials designed to document clinical efficacy and safety. The total cost for development of a new anti-infective drug is estimated to be 500–600 million Euros, and is rarely completed in less than 4–6 years after the first administration to human beings.

Most of the developing nations license and make available only antimalarial drugs that are provided through national health programmes. Baird<sup>42</sup> has mentioned that this approach often excludes relatively expensive or risky therapies, even for patients who may be able to afford a given drug and have access to medical supervision. He further observes that the main factor affecting antimalarial drug availability is economic. The developing world requires distribution strategies for effective therapies that overcome the availability of cheap but ineffective drugs.

### IP challenges

Commercializing an antimalarial technology raises significant IP challenges. Overlapping claims of different patents may cover antimalarial compounds and antigens that may be needed for drug or vaccine development. Such concentration of patents with potentially overlapping claims results in patent thicket. Such a patent thicket is daunting because it is likely that more than one compound or antigen would be needed for an effective vaccine or drug. A solution to patent thicket is through traditional licensing or partnering, which will tie up resources needed to develop and deliver the drugs and vaccines. The Malaria Vaccine Initiative (MVI) used this solution to circumvent a patent thicket associated with the primary malaria antigen vaccine candidate *P. falciparum* MSP-1. MVI contracted Alta Biomedical Group LLC to identify potential patent roadblocks associated with MSP-1. Up to 39 patent families, owned by 21 organizations (80% private sector, 20% public sector) were identified, of which researchers will need to negotiate with at least eight entities for access. Although these patents were an early disincentive for vaccine manufacturers to invest in malaria vaccine development, early identification facilitated informed decision making for strategic IP management<sup>43</sup>.

A drawback of this method is that the negotiation required to access the key patents could delay the delivery of the antimalarial agents. Another possibility is that access to key patents may not be available, which would affect investment decision upstream in the development pipeline. As a result, it may not be possible to pursue the effective drug or vaccine candidate, if companies holding valuable malaria-drug/vaccine IP are unwilling to license to others even if they are not developing a malaria drug/vaccine themselves. Accessing the availability to key patents becomes a priority<sup>44</sup>.

### Concluding remarks

Malaria is an extremely difficult disease that has eluded modern science for a long time. Recent advances, however, are promising. A difficult situation has arisen in view of the development of resistance of the parasite to antimalarials and unavailability of a vaccine. But by working around these problems we can achieve suitable and acceptable solutions to these situations. Resistance to single-drug therapies can be overcome by using them in a combination therapy. Mathematical modelling predicts that existing drugs should be used in combination if their effectiveness is to be safeguarded<sup>45</sup>. The precise choice of combinations and formulation requires an immediate research effort. The formulation, packaging, deployment and adherence to these new compounds should be studied. Such studies require only a small investment compared with the cost of developing new drugs<sup>46</sup>. IP challenges should be addressed and resolved so that access to the drugs, to be used in combination, is available. Lastly, initiatives like patent pool should be considered as complements to a broad set of other policies that are needed to ensure access to medicine for all; patent pools are only one way of addressing the issue.

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