We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Plasmodium vivax and *Plasmodium ovale* in the Malaria Elimination Agenda in Africa

Isaac K. Quaye and Larysa Aleksenko

Abstract

In recent times, several countries in sub-Saharan Africa have reported cases of *Plasmodium vivax* (*Pv*) with a considerable number being Duffy negative. Current efforts at malaria elimination are focused solely on *Plasmodium falciparum* (*Pf*) excluding non-falciparum malaria. *Pv* and *Plasmodium ovale* (*Po*) have hypnozoite forms that can serve as reservoirs of infection and sustain transmission. The burden of these parasites in Africa seems to be more than acknowledged, playing roles in migrant and autochthonous infections. Considering that elimination and eradication is a current aim for WHO and Roll Back Malaria (RBM), the inclusion of *Pv* and *Po* in the elimination agenda cannot be over-emphasized. The biology of *Pv* and *Po* are such that the same elimination strategies as are used for *Pf* cannot be applied so, going forward, new approaches will be required to attain elimination and eradication targets.

Keywords: *Plasmodium vivax* transmission, *Plasmodium ovale*, asymptomatic transmission, sub-Saharan Africa

1. Introduction

Malaria elimination is defined as interruption of local transmission of malaria in a defined area [1, 2]. Within a geographical demarcation, malaria transmission is heterogenous ranging between high, intermediate or low [3, 4]. This means that elimination efforts must be defined with respect to the geographical area, and interventions targeted to specified strata to achieve elimination goals [5, 6]. Data for such targeted intervention can come from the use of sensitive and specific surveillance diagnostic tools that can discriminate between species, including asymptomatic infections. In Africa, current efforts of intervention by National Malaria Control Programs and recommendation by WHO and Roll Back Malaria (RBM) are focused mainly on *Plasmodium falciparum* (*Pf*) with little to no attention on non-falciparum species although the latter are established to be present in all of Africa [7, 8]. Clearly if elimination is envisaged based on the target of RBM, then inclusion of all human *Plasmodium* species in the elimination agenda is relevant. Non-falciparum *Plasmodial* species are more complicated in their transmission than *Pf* [9–11]. Especially, *Plasmodium vivax* (*Pv*), that is the most prevalent in the world and the two sympatric species of *Plasmodium ovale* (*Po*), *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri* both of which cause severe disease and have

hypnozoite stages in their transmission cycle as *Pv* [12–15]. The inclusion of all species should be well planned in such a way that it does not take away from the efforts being made to reduce *Pf* transmission but to go hand in hand. The transmission dynamics of these species must be well understood so that measures tailored to them are put in place. Here aspects of the biology of the parasites are elaborated so they are put in perspective with regards to elimination.

2. Biology of *Pv* and *Po*

Plasmodium species are obligate intracellular parasites that infect *Anopheles* mosquitoes in the sexual life cycle and humans in their asexual life cycle [16]. In humans, replication takes place in the liver hepatocytes, following inoculation by an infected *Anopheles* mosquito into the skin, and migration of the parasite through the capillaries into the blood stream and then to the liver parenchyma cells [17]. This pattern of infection is similar in all known human *Plasmodium* parasites which currently are *P. falciparum*, *P. vivax*, *P. ovale curtisi*, *P. ovale wallikeri*, *P. malariae* and *P. knowlesi* [18].

Outside of Africa, *Pv* is the predominant parasite, but even so the phenotypic characteristic from individuals infected with the parasite from different populations appear to differ. One of the most important differences between plasmodial species infecting humans is the ability of *Pv* and *Po* to relapse after the cure of the original infection [9, 12]. A proportion of sporozoites do not undergo immediate development in the invaded hepatocytes. Instead, they remain dormant in the liver as hypnozoites for prolonged periods of time before developing and causing recurrent infection [19]. *P. vivax* strains from different geographical areas show widely different relapse patterns, reflecting evolutionary adaptation to local environmental conditions that optimize transmission potential of the parasite [20]. In Africa, it had previously been generally accepted that because of the high prevalence of ACKR1 polymorphism, individuals of African descent are resistant to infection by the parasite [21]. Recent evidence of *Pv* presence in nearly the whole of Africa, indicates that *Pv* may have other mechanisms for invasion [22]. Advancing research into the parasites' biology and mechanism of invasion is necessary for elimination and eradication. Although *Po* is not limited by the Duffy antigen polymorphism, the shared biology of hypnozoites and their relapse makes it of equal concern in malaria elimination. What is palpably clear is that reporting of these two parasites from countries in Africa, appears not to reflect the true prevalence rate as reporting is largely passive and not active.

2.1 Parasite transmission

Transmission of the parasite defines the processes that the parasite takes to complete a life cycle [1]. The process in the *Anopheles* vector is referred to as sporogony while that in humans is referred to as schizogony. Schizogony begins when liver schizonts which contain multiples of merozoites mature and burst with subsequent release of the merozoites into the blood stream [23]. The merozoites invade young reticulocytes that have the surface marker CD71(CD71⁺) [24] where they mature into trophozoites. The trophozoites mature into blood stage schizonts containing multiples of merozoites, burst the reticulocytes and initiate a new cycle of blood stage transmission. Some of the merozoites mature into male and female gametocytes that are picked by female *Anopheles* mosquitoes when mature, to begin the sporogonic cycle [1]. In *Pv* and *Po* some of the liver schizonts remain dormant for weeks, months or years and then get activated to initiate a new infection in the

reticulocytes [16]. It is not clear what exactly triggers the reactivation, although new *Plasmodium* and other infections and inflammation, have been suggested as contributory [9, 25]. The subsets that remain in the liver are the hypnozoites, and the reactivation process is called 'relapse'. The activation of hypnozoites is reported to cause most of the blood stage infections [26]. It is not clear whether the under-reporting of *Pv* and *Po* infections in Africa is attributed to hypnozoites relapsing or lack of tools or focus for targeting these species for detection.

It has been reported that the hypnozoites are not only derived from liver parenchyma cells, but also from bone marrow parenchyma that abounds in young and CD71⁺ reticulocytes [24]. It has been shown that the bone marrow is enriched in gametocytes extravascularly, while the liver is enriched with tissue schizonts in the sinusoids compared to peripheral blood [24]. In addition, a small number of parasites are seen in the vasculature of the lungs as opposed to those in the bone marrow and liver which are extravascular [27]. The hypnozoite stages are particularly troubling because chemotherapy against them with the use of primaquine is restrictive due to glucose-6-phosphate dehydrogenase deficiency and CYP2D6 polymorphism [28]. Also, it has been reported that primaquine may not be efficacious against some strains of the hypnozoite stages [29]. Nevertheless, radical cure with primaquine at least can go a long way in the agenda towards elimination.

2.2 Hypnozoite stages

Previously there was no direct evidence of hypnozoite stages of *Po*, however recent reports have clearly shown that such stages indeed exist for both *Po curtisi* and *Po walikeri* [30]. The sub-species of the parasite contribute to the transmission dynamics and need to be fully interrogated for markers and drug targeting. Another unique biology of the parasite is the early emergence and maturation of gametocytes in the blood. While gametocytes for *Pf*, *Pm* mature in about 10–12 days, for *Pv* and *Po*, gametocytes are seen between 3 to 5 days following the first documentation of parasites in the peripheral blood [1, 16, 23]. This means even before any symptoms of infection are seen the parasite would have been transmitted if female *Anopheles* mosquitoes fed within the period. In this case an intervention in the transmission process can be missed. It maybe that these traditionally unseen parasites, contribute to the low parasitemia usually seen with these infections and why *Pv* and *Po* infections are characterized as benign although they can cause as much severe disease as in *Pf* infections.

2.3 Transmission dynamics

In regions outside of sub-Saharan Africa (SSA) where *Pf* and *Pv* coexist, mixed-species infections are common [31]. In such situations, there are observed shifts in the dominant parasite towards *Pv* as *Pf* transmission declines. Surveys usually report rates less than 2% and yet careful clinical studies record rates of up to 30% and this figure is even higher when PCR detection methods are used. This trend means that in a couple of years to come, without effective and necessary interventions, when the *Pf* burden has been significantly reduced in Africa, *Pv* and *Po* infections could constitute the most dominant *Plasmodium* species on the continent. We observe that countries that were on course for *Pf* elimination such as Botswana, eSwatini, and South Africa have seen changes recently, part of which is due to *Pv* and *Po*. Concurrent infections with different *Plasmodium* species may have important implications on the host response and development of cross-species immunity. The potential for *Pv* to attenuate *Falciparum* malaria obviously requires further characterization and has significant implications for vivax-only vaccination strategies, and the deployment of drugs such as chloroquine, which has lost efficacy

against *Pf* but still retain it against *Pv*. The transmission of the parasite in Duffy negative individuals raises serious concern as essentially *Pf* is the only targeted species in the elimination agenda in Africa, with minimal consideration for *Pv* and *Po*.

2.4 What is needed currently on *Pv* and *Po* transmission?

As noted previously, *Pv* and *Po* can cause severe disease [13, 15]. The most characteristic of *Pv* are acute respiratory distress syndrome (ARDS), anemia and decreased oxygen saturation in both children and adults [32, 33]; clinical conditions which are also seen in *Po* infections [34–36]. The respiratory illnesses are associated with high mortality, with a higher risk in women. In the cited *Po* cases of ARDS, the patients were also HIV positive, so it is not clear if HIV facilitated development to full blown ARDS or not [32, 37]. The new tissue sequestration sites of *Pv* and *Po* mentioned previously, which are out of routine diagnostic procedures, means the task of eliminating *Pv* and *Po* is clearly not an easy one. When the unique biology of *Pv* and *Po* vis-à-vis the evidence of their presence in Africa are considered, there is a need for a paradigm shift regarding *Pv* and *Po* research by putting in place the following:

1. Sensitization of National Malaria Control Programs (NMCPs) to the menace of the two parasites in asymptomatic and symptomatic infections
2. Provision of baseline and standardized tools for sample collection, detection and assays for *Pv* and *Po* towards the elimination of the parasites.
3. Measures for all individuals irrespective of age in Africa to be at reduced risk to *Pv* and *Po* infections
4. De-escalation of the burden of *Pv* and *Po*, through the utilization of novel and available tools that can be integrated into malaria control and elimination agenda in sub-Saharan Africa.
5. Crosstalk between NMCPs and researchers as well as institutions engaged in malaria research.
6. Creation of fora for exchange of knowledge and resources between *Pv* and *Po* focused scientists in Africa and globally, to facilitate progress in control and elimination activities.

3. Conclusion and future perspectives

The presence of *Pv* and *Po* in Africa is certain. Malaria control programs generally focus on providing good vector control, early diagnosis, and access to effective antimalarial regimens, preferably with anti-gametocyte activity to reduce transmission. All these tools cannot be optimally employed without a knowledge of the transmission dynamics of all parasites within a community or country. Re-engaging the focus of NMCPs on non-falciparum malaria that harbor hypnozoites and that potentially could be a significant problem in the very near future is a necessity. Pooling of resources regionally and internationally are key elements for the fight against reducing the burden of non-falciparum malaria and their elimination. It is important that NMCPs and researchers from Universities and Research Institutions engage in crosstalk to facilitate accurate detection and surveillance, and generate the human resource required for sustaining these efforts.

Acknowledgements

The authors acknowledge the patience and support of the Intech Open team and our entire family in the write up.

Conflict of interest

The authors declare no conflict of interest.

Author details

Isaac K. Quaye^{1*} and Larysa Aleksenko²

¹ Department of Applied Health Sciences, Regent University College of Science and Technology, Accra, Ghana

² Division of Obstetrics and Gynecology, Department of Clinical Sciences, Faculty of Medicine, Lund University, Lund, Sweden

*Address all correspondence to: isaac.quaye@regent.edu.gh

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] S.K. Nilsson, L.M. Childs, C. Buckee, M. Marti, Targeting Human Transmission Biology for Malaria Elimination, *PLoS Pathog.* 11 (2015) e1004871.
- [2] J.M. Cohen, B. Moonen, R.W. Snow, D.L. Smith, How absolute is zero? An evaluation of historical and current definitions of malaria elimination, *Malar J.* 9 (2010) 213-2875-9-213.
- [3] M.E. Woolhouse, Patterns in parasite epidemiology: the peak shift, *Parasitol. Today.* 14 (1998) 428-434.
- [4] T. Bousema, J.T. Griffin, R.W. Sauerwein, D.L. Smith, T.S. Churcher, W. Takken, A. Ghani, C. Drakeley, R. Gosling, Hitting hotspots: spatial targeting of malaria for control and elimination, *PLoS Med.* 9 (2012) e1001165.
- [5] T. Bousema, G. Stresman, A.Y. Baidjoe, J. Bradley, P. Knight, W. Stone, V. Osoiti, E. Makori, C. Owaga, W. Odongo, P. China, S. Shagari, O.K. Doumbo, R.W. Sauerwein, S. Kariuki, C. Drakeley, J. Stevenson, J. Cox, The Impact of Hotspot-Targeted Interventions on Malaria Transmission in Rachuoonyo South District in the Western Kenyan Highlands: A Cluster-Randomized Controlled Trial, *PLoS Med.* 13 (2016) e1001993.
- [6] T. Bousema, B. Kreuels, R. Gosling, Adjusting for heterogeneity of malaria transmission in longitudinal studies, *J. Infect. Dis.* 204 (2011) 1-3.
- [7] A.A. Lover, J.K. Baird, R. Gosling, R.N. Price, Malaria Elimination: Time to Target All Species, *Am. J. Trop. Med. Hyg.* 99 (2018) 17-23.
- [8] K.A. Twohig, D.A. Pfeffer, J.K. Baird, R.N. Price, P.A. Zimmerman, S.I. Hay, P.W. Gething, K.E. Battle, R.E. Howes, Growing evidence of *Plasmodium vivax* across malaria-endemic Africa, *PLoS Negl Trop. Dis.* 13 (2019) e0007140.
- [9] N.J. White, Determinants of relapse periodicity in *Plasmodium vivax* malaria, *Malar J.* 10 (2011) 297-2875-10-297.
- [10] B.M. Greenwood, Asymptomatic malaria infections--do they matter? *Parasitol. Today.* 3 (1987) 206-214.
- [11] C. Doderer-Lang, P.S. Atchade, L. Meckert, E. Haar, S. Perrotey, D. Filisetti, A. Aboubacar, A.W. Pfaff, J. Brunet, N.W. Chabi, C.D. Akpovi, L. Anani, A. Bigot, A. Sanni, E. Candolfi, The ears of the African elephant: unexpected high seroprevalence of *Plasmodium ovale* and *Plasmodium malariae* in healthy populations in Western Africa, *Malar J.* 13 (2014) 240-2875-13-240.
- [12] M. Groger, H.S. Fischer, L. Veletzky, A. Lalremruata, M. Ramharther, A systematic review of the clinical presentation, treatment and relapse characteristics of human *Plasmodium ovale* malaria, *Malar J.* 16 (2017) 112-017-1759-2.
- [13] S. Amireh, H. Shaaban, G. Guron, Severe *Plasmodium vivax* cerebral malaria complicated by hemophagocytic lymphohistiocytosis treated with artesunate and doxycycline, *Hematol. Oncol. Stem Cell. Ther.* 11 (2018) 34-37.
- [14] W.A. Krotoski, W.E. Collins, R.S. Bray, P.C. Garnham, F.B. Cogswell, R.W. Gwadz, R. Killick-Kendrick, R. Wolf, R. Sinden, L.C. Koontz, P.S. Stanfill, Demonstration of hypnozoites in sporozoite-transmitted *Plasmodium vivax* infection, *Am. J. Trop. Med. Hyg.* 31 (1982) 1291-1293.
- [15] A. D'Abramo, S. Gebremeskel Tekle, M. Iannetta, L. Scorzolini, A. Oliva, M.G. Paglia, A. Corpolongo, E. Nicastri,

Severe Plasmodium ovale malaria complicated by acute respiratory distress syndrome in a young Caucasian man, Malar J. 17 (2018) 139-018-2289-2.

[16] J.H. Adams, I. Mueller, The Biology of *Plasmodium vivax*, Cold Spring Harb Perspect. Med. 7 (2017) 10.1101/cshperspect.a025585.

[17] L.M. Yamauchi, A. Coppi, G. Snounou, P. Sinnis, Plasmodium sporozoites trickle out of the injection site, Cell. Microbiol. 9 (2007) 1215-1222.

[18] B. Singh, L. Kim Sung, A. Matusop, A. Radhakrishnan, S.S. Shamsul, J. Cox-Singh, A. Thomas, D.J. Conway, A large focus of naturally acquired Plasmodium knowlesi infections in human beings, Lancet. 363 (2004) 1017-1024.

[19] T.N. Wells, J.N. Burrows, J.K. Baird, Targeting the hypnozoite reservoir of Plasmodium vivax: the hidden obstacle to malaria elimination, Trends Parasitol. 26 (2010) 145-151.

[20] L.J. Robinson, R. Wampfler, I. Betuela, S. Karl, M.T. White, C.S. Li Wai Suen, N.E. Hofmann, B. Kinboro, A. Waltmann, J. Brewster, L. Lorry, N. Tarongka, L. Samol, M. Silkey, Q. Bassat, P.M. Siba, L. Schofield, I. Felger, I. Mueller, Strategies for understanding and reducing the Plasmodium vivax and Plasmodium ovale hypnozoite reservoir in Papua New Guinean children: a randomised placebo-controlled trial and mathematical model, PLoS Med. 12 (2015) e1001891.

[21] L.H. Miller, S.J. Mason, D.F. Clyde, M.H. McGinniss, The resistance factor to Plasmodium vivax in blacks. The Duffy-blood-group genotype, FyFy, N. Engl. J. Med. 295 (1976) 302-304.

[22] P.A. Zimmerman, Plasmodium vivax Infection in Duffy-Negative People in Africa, Am. J. Trop. Med. Hyg. 97 (2017) 636-638.

[23] E. Meibalan, M. Marti, Biology of Malaria Transmission, Cold Spring Harb Perspect. Med. 7 (2017) 10.1101/cshperspect.a025452.

[24] B. Malleret, A. Li, R. Zhang, K.S. Tan, R. Suwanarusk, C. Claser, J.S. Cho, E.G. Koh, C.S. Chu, S. Pukrittayakamee, M.L. Ng, F. Ginhoux, L.G. Ng, C.T. Lim, F. Nosten, G. Snounou, L. Renia, B. Russell, Plasmodium vivax: restricted tropism and rapid remodeling of CD71-positive reticulocytes, Blood. 125 (2015) 1314-1324.

[25] I. Mueller, M.R. Galinski, J.K. Baird, J.M. Carlton, D.K. Kochar, P.L. Alonso, H.A. del Portillo, Key gaps in the knowledge of Plasmodium vivax, a neglected human malaria parasite, Lancet Infect. Dis. 9 (2009) 555-566.

[26] A.I. Adekunle, M. Pinkevych, R. McGready, C. Luxemburger, L.J. White, F. Nosten, D. Cromer, M.P. Davenport, Modeling the dynamics of Plasmodium vivax infection and hypnozoite reactivation in vivo, PLoS Negl Trop. Dis. 9 (2015) e0003595.

[27] A. Mayor, A. Bardaji, E. Macete, T. Nhampossa, A.M. Fonseca, R. Gonzalez, S. Maculube, P. Cistero, M. Ruperez, J. Campo, A. Vala, B. Sigauque, A. Jimenez, S. Machevo, L. de la Fuente, A. Nhama, L. Luis, J.J. Aponte, S. Acacio, A. Nhacolo, C. Chitnis, C. Dobano, E. Sevens, P.L. Alonso, C. Menendez, Changing Trends in P. falciparum Burden, Immunity, and Disease in Pregnancy, N. Engl. J. Med. 373 (2015) 1607-1617.

[28] J.K. Baird, K.E. Battle, R.E. Howes, Primaquine ineligibility in anti-relapse therapy of Plasmodium vivax malaria: the problem of G6PD deficiency and cytochrome P-450 2D6 polymorphisms, Malar J. 17 (2018) 42-018-2190-z.

[29] D. Thomas, H. Tazerouni, K.G. Sundararaj, J.C. Cooper, Therapeutic failure of primaquine and need for new

medicines in radical cure of *Plasmodium vivax*, *Acta Trop.* 160 (2016) 35-38.

[30] M. Groger, L. Veletzky, A. Lalremruata, C. Cattaneo, J. Mischlinger, R. Manego Zoleko, J. Kim, A. Klicpera, E.L. Meyer, D. Blessborn, M. Winterberg, A.A. Adegnika, S.T. Agnandji, P.G. Kremsner, B. Mordmuller, G. Mombo-Ngoma, H.P. Fuehrer, M. Ramharter, Prospective Clinical and Molecular Evaluation of Potential *Plasmodium ovale curtisi* and *wallikeri* Relapses in a High-transmission Setting, *Clin. Infect. Dis.* 69 (2019) 2119-2126.

[31] P.A. Zimmerman, R.K. Mehlotra, L.J. Kasehagen, J.W. Kazura, Why do we need to know more about mixed *Plasmodium* species infections in humans? *Trends Parasitol.* 20 (2004) 440-447.

[32] E. Tjitra, N.M. Anstey, P. Sugiarto, N. Warikar, E. Kenangalem, M. Karyana, D.A. Lampah, R.N. Price, Multidrug-resistant *Plasmodium vivax* associated with severe and fatal malaria: a prospective study in Papua, Indonesia, *PLoS Med.* 5 (2008) e128.

[33] N.M. Anstey, B. Russell, T.W. Yeo, R.N. Price, The pathophysiology of *vivax* malaria, *Trends Parasitol.* 25 (2009) 220-227.

[34] K.K. Dayananda, R.N. Achur, D.C. Gowda, Epidemiology, drug resistance, and pathophysiology of *Plasmodium vivax* malaria, *J. Vector Borne Dis.* 55 (2018) 1-8.

[35] Y.L. Lau, W.C. Lee, L.H. Tan, A. Kamarulzaman, S.F. Syed Omar, M.Y. Fong, F.W. Cheong, R. Mahmud, Acute respiratory distress syndrome and acute renal failure from *Plasmodium ovale* infection with fatal outcome, *Malar J.* 12 (2013) 389-2875-12-389.

[36] S. Eiam-Ong, Malarial nephropathy, *Semin. Nephrol.* 23 (2003) 21-33.

[37] M.V. Lacerda, S.C. Fragoso, M.G. Alecrim, M.A. Alexandre, B.M. Magalhaes, A.M. Siqueira, L.C. Ferreira, J.R. Araujo, M.P. Mourao, M. Ferrer, P. Castillo, L. Martin-Jaular, C. Fernandez-Becerra, H. del Portillo, J. Ordi, P.L. Alonso, Q. Bassat, Postmortem characterization of patients with clinical diagnosis of *Plasmodium vivax* malaria: to what extent does this parasite kill? *Clin. Infect. Dis.* 55 (2012) e67-e74.