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Commentary

A novel generation of hemozoin based malaria diagnostics show promising performance

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The number of malaria cases has declined significantly over the last two decades. Approximately 6.2 million malaria deaths were prevented between 2001 and 2015 due to concerted efforts of national malaria control programs worldwide [1], currently 35 countries are aiming to move from control to elimination latest by 2035 [2]. A crucial component of all malaria control and elimination efforts is accurate malaria diagnosis at the bed side.

Malaria diagnostics are faced with a trade-off between complexity, cost, and accuracy. Polymerase chain reaction(PCR) based diagnostics have a limit of detection (LoD) of 22−1000 parasites / ml, depending on the applied assay [3,4]. However, this very low LoD comes at significant cost, a long turn around and a need for a well-developed laboratory infrastructure, attributes that do not render these methods suitable for deployment in resource poor settings were most malaria cases occur. Loop mediated isothermal amplification (LAMP) based methods provide molecular diagnosis at lower costs and with a LoD of 2000 parasites /ml, close to PCR and without the need for expensive machinery. Recent developments suggest that an even lower LoD is possible [5]. But the complex handling has hindered the broader use of LAMP based assays to date. Malaria microscopy with a hundredfold higher LoD compared to standard PCR (50−100 parasites / μl) [6] is among the most widely used malaria diagnostics worldwide and reasonably economical. However high-quality microscopy requires extensive training and continuous quality control, particularly challenging to maintain when case-loads are declining. Rapid diagnostic tests (RDTs) have been deployed widely over the last decade and address these shortfalls at a lower cost. While RDTs that detect the histidine rich protein 2 (HRP2) for the diagnosis of *P. falciparum* show sensitivities and LoDs comparable to expert microscopy, they also select for parasites with deletions of the *pfhrp2* gene, sensitivity is accordingly compromised in affected areas [7]. A novel generation of ultrasensitive RDTs with higher LoDs is being developed, but these continue to be based on HRP2. LoD of RDTs targeting *P. vivax* are significantly lower than expert microscopy [5].

Kumar and colleagues recently evaluated a novel, hemozoin based diagnostic tool (Gazelle, Hemex Health, Portland, USA) [8]. The biocrystal hemozoin is a by-product of haemoglobin digestion of the malaria parasite, formed by all five human pathogenic malaria species [9], and might prove a superior bioindicator to HRP2. The Gazelle can be operated by battery, requires 15 μl of blood, and provides a result within a minute**.** In laboratory based studies by the authors the LoD of the device was 50 parasites / μl for *P. falciparum* and 35 parasites / μl for *P. vivax,* comparable to expert microscopy and superior to current RDTs. In this study the authors compared paired results from microscopy, RDT and Gazelle to the reference method PCR in clinical samples and report a sensitivity of 82% for the Gazelle, compared to 75% for microscopy and 89% for RDT.

As of now, Gazelle cannot provide a species-specific diagnosis, which is essential information to guide malaria treatment in most countries. The practical deployment of the device is therefore limited to areas where universal malaria treatment is used [10]. The authors acknowledge this limitation and suggest that the next version of the device will be able to differentiate between *P. falciparum* and *P. vivax.*

The Gazelle is not designed as a portable device. The low LoD and its short time to diagnosis render the machine suitable for screening purposes of febrile patients in health facilities at primary health care level or at border crossings. Positive cases will then need to be differentiated to determine the correct parasite species using microscopy or RDT. If the next version can reliably differentiate malaria species, the Gazelle will fill the same niche as current routine microscopy in remote areas, however with superior operational characteristics.

Since the Gazelle does not quantify parasitaemia and does not provide information on parasite staging, the device is unlikely to play a significant role in clinical trials, where microscopy and molecular methods are more suitable.

So far, the device has been tested under highly controlled research conditions and on several hundred samples only. Subsequent studies will need to evaluate performance under real life conditions, durability with high sample load, potential for handling errors by less well-trained staff and translation of results into treatment practice. If larger field based studies provide confidence for those issues, the Gazelle is likely to be ideal for the use in remote settings.

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Author contribution

BL wrote the first draft, KT provided scientific advice and reviewed the draft.

Declaration of Competing Interest

Dr. Ley and Dr Thriemer have nothing to disclose.

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