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New beginnings for malaria research

The COVID-19 pandemic has disrupted prevention programmes for malaria and other diseases, but it has also led to new stimuli and opportunities in the development of malaria vaccines. After the pandemic, the entire field of malaria treatment and prevention can hope to overcome resistance problems and get back on course to roll back malaria. **Michael Gross** reports.

From antigen tests to zoom meetings, the COVID-19 pandemic has changed our world in various ways. Many will be keen to forget some aspects as soon as possible, but other changes will remain or at least steer society in new directions.

The medical provision for other diseases has been a serious concern, as provisions like health checks or cancer screenings were disrupted or delayed by the pandemic. In sub-Saharan Africa, there was concern that the pandemic might disrupt malaria prevention efforts. Fortunately, the latest report on malaria released by the World Health Organisation (WHO) in December shows that, after a setback in the first year of the pandemic, countries have broadly managed to hold the line against this deadly disease in the second year.

In 2021 there were an estimated 625,000 deaths from malaria, essentially unchanged from 619,000 in 2020. There had been 568,000 in 2019, the last year before the pandemic. As before, most cases and deaths occurred in Africa, with children under five carrying the highest risk of death. In the years 2015 to 2019, progress in the WHO's efforts to roll back malaria had noticeably stalled to the extent that new ideas were urgently needed (Curr. Biol. (2019) *29*, R301–R303).

In part, the problems encountered before the pandemic were due to both the parasite and the vector evolving adaptations to the measures that had previously brought success and are now in widespread use, including artemisinin-based combination therapies and insecticide-treated bednets. Additional worries have now arisen from the spread of an urban-adapted mosquito vector, *Anopheles stephensi*, from Asia into Africa. This species has been linked to the recent outbreak in the Ethiopian city of Dire Dawa and could cause considerable harm if it reaches megacities elsewhere in Africa (Curr. Biol. (2022) *32*, R1325–R1328).

Conceivably, the situation could get worse, and, even at the current plateau, the latest figures obviously represent an unacceptable burden on the health of the African population. Nevertheless, the WHO manages to extract a cautious note of optimism from the data, as the established preventative measures are back on track and new weapons against the disease, including vaccines, are becoming available.

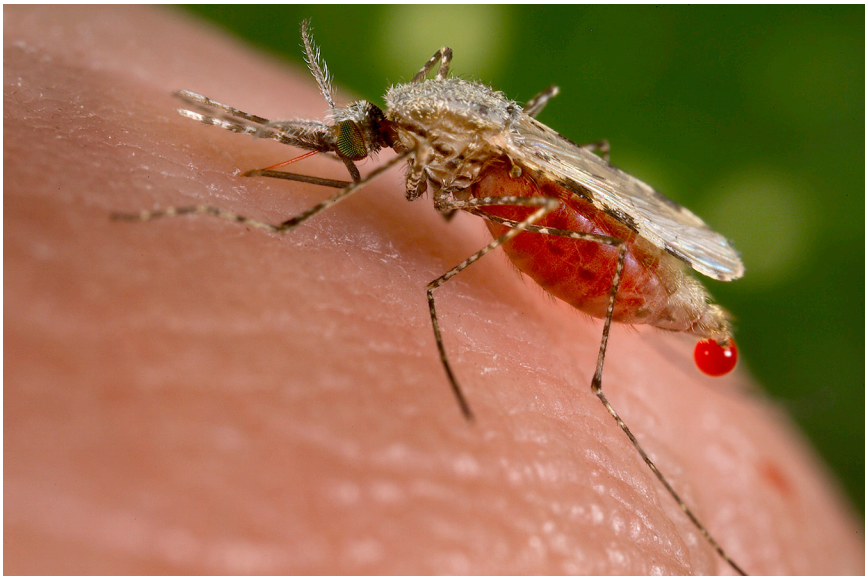
"We face many challenges, but there are many reasons for hope," WHO Director-General Tedros Adhanom Ghebreyesus said. "By strengthening the response, understanding and mitigating the risks, building resilience and accelerating research, there is every reason to dream of a malaria-free future."

Vaccination hopes

The world's first malaria vaccine, RTS,S (trade name Mosquirix), gained WHO approval in October 2021 after a pilot vaccination scheme carried out in Kenya, Malawi and Ghana. It is given in three doses to children under the age of two, with a fourth dose potentially expanding the protection, which would otherwise wane after 18 months. Currently, the rollout of the vaccine is aimed at children in mid- to high-risk areas. It reduces hospital admissions for severe malaria by around 30%, a modest efficacy that does save lives but also leaves room for improvement.

Thanks to the exceptional research effort that produced the COVID-19 vaccines, additional vaccination options may soon become available. On December 23, 2022, the German company BioNTech, whose mRNA vaccine against COVID-19 was globally marketed by Pfizer, announced a small phase 1 clinical trial for a new mRNA vaccine candidate against malaria.

The trial to be conducted in the US on 60 healthy volunteers is part of the BNT165 programme to develop multi-antigen vaccine candidates against *Plasmodium falciparum*, which is the deadliest version of the malaria parasite. BioNTech aims to identify an optimal antigen to target with mRNA vaccines.



Blood red: Blocking the transmission of viable malaria parasites between mosquitoes and humans is an important part of the effort to roll back malaria. The photo shows *Anopheles stephensi*, a mosquito species that is native to Asia but has recently been linked to urban outbreaks of malaria in Africa. (Photo: Jim Gathany.)

Lab box: For its forthcoming malaria vaccines, the German biotech company BioNTech is developing portable production facilities that can be deployed in Africa where the vaccines are needed. (Photo: © BioNTech SE 2023, all rights reserved.)

Simultaneously, the company is also working towards creating mobile production facilities to be deployed in Africa so vaccines and other pharmaceuticals can be made where they are needed. The concept is based on a laboratory fitted inside a container, dubbed the BioNTainer. The first containers are ready for deployment and could thus serve to produce malaria vaccine *in situ* as soon as its development has been concluded successfully.

In a separate effort, the group of Nirbhay Kumar at George Washington University, at Washington DC, USA, has tested two mRNA vaccine candidates in mice (NPJ Vaccines (2022) *7*, 155). The researchers found that both vaccines, targeting separate parts of the infection process, effectively prevent disease and onward transmission in the animal model. Optimal results can be achieved by administering both mRNAs together. Kumar and colleagues are now working towards testing their candidates in primate models and then in humans.

Elsewhere, the US-based biotechnology company Novavax is also transferring lessons learned in the COVID-19 pandemic to the field of malaria vaccines. The company has developed the adjuvant Matrix-M, which consists of nanoparticles made from saponins extracted from *Quillaja saponaria* (soapbark) trees, cholesterol, and phospholipids, for use in its COVID-19 vaccine NVX-CoV2373, which has gained full authorisation in Australia, Canada, Japan, and South Korea, as well as emergency approval in many other countries. Matrix-M is also part of their R21 malaria vaccine candidate, a protein-based vaccine that is currently undergoing a phase 2b clinical trial. In an earlier phase 2 trial, R21/Matrix-M had achieved 77% efficacy, making it the most effective malaria vaccine yet.

Another coronavirus vaccine currently in development may also lead to a spin-off product against malaria. Merel Smit at Radboud University, Netherlands, and colleagues, together with the Danish biotechnology company AdaptVac have developed a novel vaccine against coronaviruses based on virus-like particles that can be covered with antigens specific to the pathogen it is meant to target. The researchers recently reported the results of a successful phase 1 clinical trial (Lancet Microbe (2023) https://doi.org/10.1016/S2666-5247(22)00337-8). On the same platform, the researchers are also developing a malaria vaccine that they hope to be able to test in 2024.

Yet another vaccine candidate has recently been shown to be effective in adults who have had previous infections with malaria. The group of Matthew Laurens at the University of Maryland, USA, reported a clinical trial of the *Plasmodium falciparum* sporozoite (PfSPZ) vaccine involving a placebo-controlled challenge study showing that the vaccine, given as three injections, has at least 46% efficacy for a period of 18 months (Sci. Transl. Med. (2022) *14*, 3776). This vaccine is based on inactivated forms of the sporozoite, the life stage that develops in the mosquito and then infects new hosts. Future research will also address whether this vaccine is suitable for the population groups most vulnerable to malaria, especially young children.

New research tools

In addition to the new vaccine hopes, several other fields relating to the prevention or treatment of malaria have seen hopeful buds of a new beginning after the setback of the pandemic. Even the oldest treatment option for malaria, quinine, may be getting a fresh start. Quinine is an alkaloid extracted from the bark of cinchona trees (genus *Cinchona*), native to Peru. Before colonisation, the Quechua knew of the medicinal properties of the bark, which they ground up and mixed with sweetened water. Even today, extraction from the plant remains the only production route that is commercially viable.

The chemical synthesis of quinine is extremely challenging, due to the presence of four asymmetric centres, potentially giving rise to 16 different isomeric forms. Chemists have found several routes to make the molecule, but all of them are too difficult to be much use for pharmaceutical applications. Now Takahiro Terunuma and Yujiro Hayashi at Tohoku University, Japan, have presented a relatively simple path using organocatalysts and five one-pot reactions with as many purification steps (Nat. Commun. (2022) *13*, 7503). The overall yield amounts to 14%. Even though this is not going to be an alternative to the extraction of the natural product, the authors hope that it may pave the way to new derivatives of quinine and thus stimulate new research and development into novel anti-malaria substances.

In another boost to drug research and vaccine development, the group of Stephen Hoffman at the biotechnology company Sanaria in Rockville, USA, has reported the successful breeding of *P. falciparum* sporozoites *in vitro*, without the need for mosquitoes or a

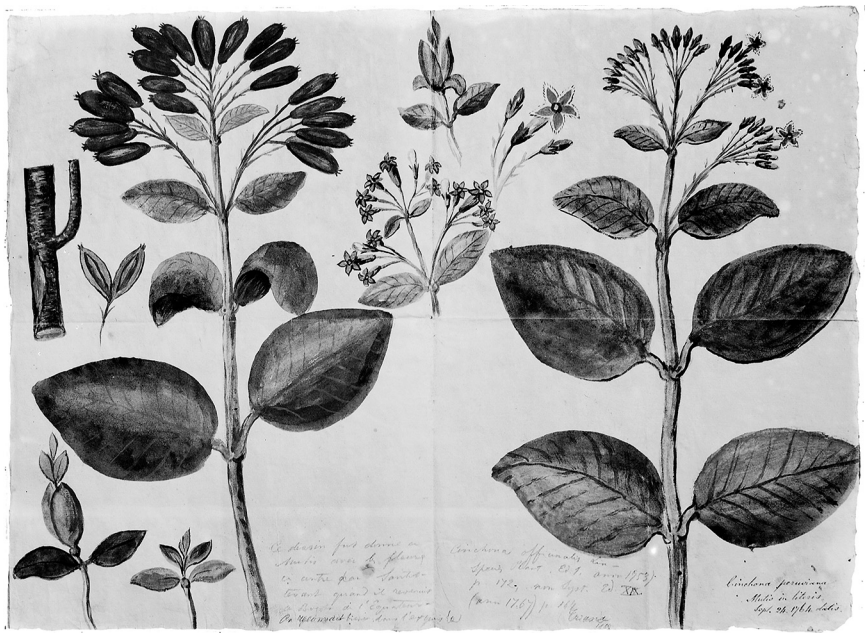
mammalian host (Nature (2022) *612*, 534–539). As the name Sanaria cleverly suggests, the company is focused on malaria and committed to eliminating the disease by vaccinations. The company's breakthrough in sporozoite production already benefits the industrial production of its PfSPZ vaccines like the one mentioned above, but it should also facilitate research on the parasite more widely, including the testing of treatment options.

Prevent or treat

In the spirit of finding new methods to bypass the resistance problems that are limiting the success of established prevention methods, Kirsten Lyke from the University of Maryland and colleagues undertook a small clinical study for the use of small doses of a monoclonal antibody designed to prevent malaria in people exposed to the risk (Lancet Inf. Dis. (2023) https://doi.org/10.1016/S1473-3099(22)00793-9). The researchers used a placebo-controlled challenge study to demonstrate the effectiveness of the treatment in preventing disease. Whereas all participants in the control group contracted malaria in the experiment, only four out of the seven participants who had received the antibody treatment six months earlier did so.

Monoclonal antibody treatments can be expensive, so the effectiveness of a very low dose is good news. "While previous research suggests that monoclonal antibodies can be effective against malaria using higher dose intravenous infusions, this new study finds that the prophylactic treatment can also provide a high level of protection with just a single injection," said Mark Gladwin from the University of Maryland School of Medicine. "That's a potential game changer that could provide a practical way to deploy monoclonal antibody therapies in African countries."

Even the treatment of patients already infected can help to stop the spread of the disease, as these patients can become the source of new *Plasmodium* life cycles and thus produce new infections. In a drug screen for possible agents that might interrupt the cycle, the group of Jake Baum at Imperial College London, UK, identified in 2018 a series of molecules from the family of sulphonamides that were effective in blocking transmission. After further work to identify promising lead compounds, the group has now reported a detailed study of how some of these sulphonamides interfere with the reproductive cycle of the parasite (Dis. Model. Mech. (2023) *16*, dmm049950).



Old bark: Quinine is found in the bark of cinchona trees. Their medicinal properties were known to the Quechua in Peru since before colonial times. The photo shows the watercolour the Spanish botanist José Celestino Mutis sent to Linnaeus in 1764. (Photo: Wellcome Collection (CC BY 4.0).)

Specifically, the researchers studied how the N-4HCS compounds prevent formation of male gametes from gametocytes in the mosquito gut after transmission. With photoaffinity labelling and mass spectrometry, they identified the *P. falciparum* gametocyte membrane protein Pfs16 as the target of the sulphonamides.

First author Sabrina Yahiya commented that "targeting parasite transmission from human to mosquito and back again is pivotal if we hope to reach the goal of worldwide malaria elimination. If you only treat one symptomatic patient, you address their symptoms but neglect the issue of malaria spread. By limiting transmission, however, you can radically curtail the spread of malaria across a population".

One drawback of the application in malaria patients is that the blocking effect only lasts a short while, on the order of six minutes. Therefore, an active concentration of the substance in the bloodstream would have to be maintained to ensure that any mosquitoes biting the patient only get blocked parasites. A possible alternative that the researchers also want to investigate would be to use the sulphonamides directly against the mosquitoes, such as on bednets or on bait.

"Altogether, there is an evident need to divert from existing strategies and to focus on innovation and novelty in malaria containment and management," Yahiya said in an interview accompanying the publication. "Promisingly, leading industry and academic groups are focusing research efforts on improvements to vaccine efficacy and drug-screening campaigns. There is also a huge amount of innovation within the malaria research community, with exciting new approaches to vector control, parasite killing, disease diagnostics, vaccine approaches and monoclonal antibody therapies."

Thus, although the situation on the ground is still a public health crisis by anybody's standards, the research and development sprouting into many new directions are offering a real sense of hope.

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