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Viewpoint

Immunomodulation through vaccination as a promising therapeutic strategy to mitigate malaria-related neurocognitive sequelae

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ABSTRACT

Malaria, an ancient infectious parasitic disease, is caused by protozoa of the genus *Plasmodium*, whose erythrocytic cycle is accompanied by fever, headache, sweating and chills and a systemic inflammation that can progress to severe forms of disease, including cerebral malaria. Approximately 25% of survivors of this syndrome develop sequelae that may include neurological, neurocognitive, behavioral alterations and poor school performance. Furthermore, some outcomes have also been recorded following episodes of non-severe malaria, which correspond to the most common clinical form of the disease worldwide. There is a body of evidence that neuroinflammation, due to systemic inflammation, plays an important role in the neuropathogenesis of malaria culminating in these cognitive dysfunctions. Preclinical studies suggest that vaccination with type 2 immune response elicitors, such as the tetanus-diphtheria (Td) vaccine, may exert a beneficial immunomodulatory effect by alleviating neuroinflammation. In this viewpoint article, vaccination is proposed as a therapy approach to revert or mitigate neurocognitive deficits associated with malaria.

Malaria is an infectious parasitic disease of tropical and subtropical regions that had its transmission consolidated among humans probably about 10,000 years ago, when humans began to dedicate themselves to agriculture and to be in intense contact with the mosquito vectors. A poverty-associated disease, it is estimated that malaria caused in 2020 241 million clinical cases and 671,000 deaths (WHO, 2021). Its most frequent clinical presentation is non-severe malaria (nSM), with symptoms such as fever, chills and headache. However, the disease can progress to severe forms as cerebral malaria (CM) that, in endemic regions, affect mainly children and non-immune individuals, with acute and long-term implications.

One quarter of the CM survivors may develop neurocognitive alterations as sequelae. Long-term alterations in attention, learning, memory, executive function and even internalizing and externalizing problems are evidenced. However, even nSM may impact cognitive function, as highlighted by the occurrence of verbal comprehension, working memory and school performance deficits in endemic areas with predominance of *Plasmodium vivax* transmission and where severe malaria is rare (Vitor-Silva et al., 2009; Tapajós et al., 2019; Pessoa et al., 2022). Children, adults and elderlies can be affected (Rosa-Gonçalves et al., 2022a; Pessoa et al., 2022).

The standard treatment for malaria is focused on rapidly eliminating the parasite, at the blood or hepatic stages, with potent antimalarial drugs such as the artemisinin combined therapies and primaquine. Specific supportive interventions are used in particular circumstances, such as blood transfusion for severe anemia. Adjunctive therapies aiming to improve survival outcomes in other severe disease manifestations such as CM, or to decrease long-term neurocognitive deficits in affected individuals, are not available and are desperately needed. Basic research is necessary to identify potential targets for effective adjunctive therapies (Carvalho et al., 2014).

Parasite-derived and host-produced factors released into the circulation during the erythrocytic cycle induce a systemic pro-inflammatory state that can progress to neuroinflammation and result in neurocognitive damage (Fernander et al., 2022). Neuroinflammation can, therefore, represent a therapeutic target for the malaria associated

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neurocognitive dysfunction (Fernander et al., 2022; Rosa-Gonçalves et al., 2022a). Indeed, immunomodulation has recently emerged as a promising strategy to treat cognitive and behavioral sequelae in preclinical models of malaria (Rosa-Gonçalves et al., 2022a) (Fig. 1).

Plasmodium berghei ANKA infected C57BL/6 mouse is the most commonly employed preclinical model for simulating the pathology of human *Plasmodium falciparum* malaria both in severe (CM) and non-severe (nSM) disease states (de Sousa et al., 2018; Rosa-Gonçalves et al., 2022a). This model exhibits aspects of cognitive and behavioral performance close to the falciparum malaria outcomes.

Using this model, de Sousa et al. (2021) showed that sequential injections with a combination of immunogens, such as the *P. falciparum* recombinant merozoite surface protein 3 (*Pf*MSP3), ovalbumin, LPS and, the Tetanus-diphtheria (Td) and Influenza vaccines, improved the cognitive performance of animals treated for nSM and that were shown to be compromised in tests to assess recognition memory and anxiety-like behavior 80 days after treatment. The improvement in the animal's memory and behavior was also observed with the administration of stimuli eliciting a type 2 (Th2) immune response (*Pf*MSP3, ovalbumin and Td vaccine), but not after administration of LPS and influenza vaccine, stimuli that induce a Th1 response. Recently, Rosa-Gonçalves et al. (2022b) demonstrated that immunization with the Td vaccine alone could reverse deficits in recognition memory and anxiety-like behavior in animals after experimental nSM.

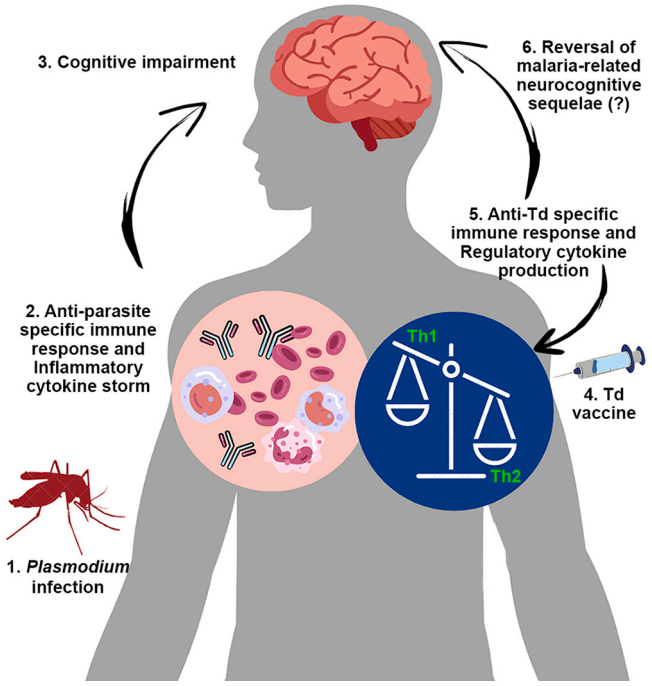

Fig. 1. Can the stimulation of the immune system by vaccination improve cognition and mitigate neurocognitive sequelae of malaria? Plasmodial infection (**1**) promotes a specific antiparasitic immune response with elevated levels of peripheral and cerebral pro-inflammatory cytokines (**2**), such as TNF, IFN and IL1-β, that are associated with impairment of brain function and of cognitive abilities (**3**). On the other hand, the stimulation of the immune system with the Td vaccine, an elicitor of Th2 responses (**4**), generates a specific immune response and induces the production of regulatory cytokine. Regulatory immune responses associated with increased levels of T-reg cells and IL-10, in the spleen and peripheral circulation (**5**), was demonstrated in mice immunized with Td (after treatment of non-severe malaria) that also showed better neurocognitive performance than non-inmmunized mice. Therefore, it is reasonable to assume that the immune response generated by Td vaccination may attenuate neurocognitive sequelae (**6**) resulting from human malaria, in the same way it does in preclinical studies in the murine experimental model (de Sousa et al., 2021; Rosa-Gonçalves et al., 2022b).

The Td human vaccine is an inexpensive preparation with low amounts of diphtheria toxoid for ages of 7 years and older, recommended by WHO. Babies need three shots of the DT (diphtheria-tetanus vaccine with regular amount of the diphtheria component) associated with the acellular pertussis vaccine (2, 4 and 6 months of age), to acquire full protective immunity against diphtheria, tetanus, and whooping cough, and then receive two booster shots (15–18 months and 4–6 years of age), to maintain the acquired protection through early childhood. Preteens and teens, pregnant women and adults (at each 10 years) must also be revaccinated with the Td. Since the association of the two anatoxins in a single vaccine capable of immunizing against both bacteria occurred as early as in 1940, it has been applied probably billions of times in the planet and corresponds therefore to one of the most largely used and safe vaccines in use nowadays.

Vaccination as a strategy to prevent cognitive decline and as cognitive enhancer has also been reported in neurodegenerative conditions. Routine vaccinations, including against tetanus and diphtheria, have been associated with reduced risk of dementia in observational studies (Wu et al., 2022). In a preclinical model of Alzheimer's disease, the *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) vaccination alleviated neuroinflammation and reversed cognitive damages (Zuo et al., 2017). This approach is being tested in a clinical trial (NCT05004688).

Some immunoregulatory mechanisms to control neuroinflammation seem to be common among these immunotherapeutic approaches. The reversal of cognitive dysfunction after malaria by stimuli that elicit a Th2 immune response, including the Td vaccine, was associated with increased serum levels of interleukin (IL) - 10 and increased regulatory T cells in the spleen (de Sousa et al., 2021). Increased levels of IL-10 in the brain were also associated with cognitive improvement after BCG vaccination in animals with Alzheimer's disease, in addition to enhanced recruitment of inflammation-resolving monocytes through the choroid plexus and perivascular spaces (Zuo et al., 2017).

The evidence in preclinical models supports applying Td vaccine in clinical trials to determine the benefit of this intervention to prevent or reverse malaria-related neurocognitive deficits (Fig. 1). Initially, trials could focus on children that experienced nSM and be performed in areas of low malaria transmission. Similar evidence has yet to be produced for the benefit of the Td vaccine following episodes of severe malaria, however this is not an unreasonable assumption. The implications are tremendous: in addition to its own intrinsic benefit as a Td vaccine, with a well-established profile of safety and efficacy, this is a simple and inexpensive intervention and would not require the lengthy and costly development demanded for a new drug.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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References

Carvalho, L.J., Moreira Ada, S., Daniel-Ribeiro, C.T., Martins, Y.C., 2014. Vascular dysfunction as a target for adjuvant therapy in cerebral malaria. Mem. Inst. Oswaldo Cruz 109 (5), 577–588. https://doi.org/10.1590/0074-0276140061.

de Sousa, L.P., de Almeida, R.F., Ribeiro-Gomes, F.L., de Moura Carvalho, L.J., e Souza, T.M., de Souza, D.O.G., Daniel-Ribeiro, C.T., 2018. Long-term effect of uncomplicated *Plasmodium berghei* ANKA malaria on memory and anxiety-like behaviour in C57BL/6 mice. Parasit. Vectors 11 (1). https://doi.org/10.1186/s13071-018-2778-8.

de Sousa, L.P., Ribeiro-Gomes, F.L., de Almeida, R.F., Souza, T.M.E., Werneck, G.L., Souza, D.O., Daniel-Ribeiro, C.T., 2021. Immune system challenge improves recognition memory and reverses malaria-induced cognitive impairment in mice. Sci. Rep. 11 (1), 14857. https://doi.org/10.1038/s41598-021-94167-8.

Fernander, E.M., Adogamhe, P., Datta, D., Bond, C., Zhao, Y., Bangirana, P., Conroy, A.L., Opoka, R.O., John, C.C., 2022. Elevated plasma soluble ST2 levels are associated with neuronal injury and neurocognitive impairment in children with cerebral malaria. Pathog. Immun. 7 (1), 60–80. https://doi.org/10.20411/pai.v7i1.499.

Pessoa, R.C., Oliveira-Pessoa, G.F., Souza, B.K.A., Sampaio, V.S., Pinto, A.L.C.B., Barboza, L.L., Mouta, G.S., Silva, E.L., Melo, G.C., Monteiro, W.M., Silva-Filho, J.H., Lacerda, M.V.G., Baía-da-Silva, D.C., 2022. Impact of *Plasmodium vivax* malaria on executive and cognitive functions in elderlies in the Brazilian Amazon. Sci. Rep. 12 (1), 10361. https://doi.org/10.1038/s41598-022-14175-0.

Rosa-Gonçalves, P., Ribeiro-Gomes, F.L., Daniel-Ribeiro, C.T., 2022a. Malaria related neurocognitive deficits and behavioral alterations. Front. Cell. Infect. Microbiol. 22 (12), 829413 https://doi.org/10.3389/fcimb.2022.829413.

Rosa-Gonçalves, P., de Sousa, L.P., Maia, A.B., Ribeiro-Gomes, F.L., Gress, C.C.T.L., Werneck, G.L., Souza, D.O., Almeida, R.F., Daniel-Ribeiro, C.T., 2022b. Dynamics and immunomodulation of cognitive deficits and behavioral changes in non-severe experimental malaria. Front. Immunol. https://doi.org/10.3389/fimmu.2022.1021211.

Tapajós, R., Castro, D., Melo, G., Balogun, S., James, M., Pessoa, R., Almeida, A., Costa, M., Pinto, R., Albuquerque, B., Monteiro, W., Braga, J., Lacerda, M., Mourão, M.P., 2019. Malaria impact on cognitive function of children in a peri-urban community in the Brazilian Amazon. Malar. J. 18 (1), 173. https://doi.org/10.1186/s12936-019-2802-2.

Vitor-Silva, S., Reyes-Lecca, R.C., Pinheiro, T.R., Lacerda, M.V., 2009. Malaria is associated with poor school performance in an endemic area of the Brazilian Amazon. Malar. J. 16 (8), 230. https://doi.org/10.1186/1475-2875-8-230.

World Health Organization. 2021. World Malaria Report 2021. Geneva: World Health Organization (Licence: CC BY-NC-SA 3.0 IGO). Available at: https://www.who.int/publications/i/item/9789240040496 [Accessed October 18, 2021].

Wu, X., Yang, H., He, S., Xia, T., Chen, D., Zhou, Y., Liu, J., Liu, M., Sun, Z., 2022. Adult vaccination as a protective factor for dementia: A meta-analysis and systematic review of population-based observational studies. Front. Immunol. 3 (13), 872542 https://doi.org/10.3389/fimmu.2022.872542.

Zuo, Z., Qi, F., Yang, J., Wang, X., Wu, Y., Wen, Y., Yuan, Q., Zou, J., Guo, K., Yao, Z.B., 2017. Immunization with Bacillus Calmette-Guérin (BCG) alleviates neuroinflammation and cognitive deficits in APP/PS1 mice via the recruitment of inflammation-resolving monocytes to the brain. Neurobiol. Dis. 101, 27–39. https://doi.org/10.1016/j.nbd.2017.02.001.