Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 vaccine results might inform malaria vaccine strategies

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Interim Com-COV2 trial data evaluated two-dose COVID-19 vaccination regimens with first dose of BNT162b2 (Pfizer-BioNTech) or ChAdOx1 nCoV-19 (Oxford-AstraZeneca) alongside second dose as either homologous vaccination, heterologous NVX-CoV2373 (Novavax) vaccination, or heterologous mRNA-1273 (Moderna) vaccination.[1] These data showed that ChAdOx1 nCoV-19 vaccination followed by NVX-CoV2373 vaccination drove optimal T-cell immunogenicity and excellent antibody induction. These heterologous vaccine approach findings are now likely to be extrapolated in developing scheduling strategies for other vaccines. We are particularly interested in the potential impact of these findings on malaria vaccine strategies. Could heterologous approaches with protein-in-adjuvant boosters improve future malaria vaccine efficacy?

Malaria vaccine development is hindered by the complex life cycle and immune evasive strategies of *Plasmodium falciparum*. Like COVID-19, repeated infections with malaria are possible, presenting a challenge to the design of vaccines that can provide lifelong protection. These issues have created barriers to the goal of the so-called holy grail in malaria vaccination, a candidate that targets all key stages of the *P falciparum* life cycle, including vector stages, to reduce transmission. The WHO recommendation on Oct 6, 2021, of the use of a malaria vaccine in the form of RTS,S/AS01 (RTS,S) shows how far we have come. RTS,S stimulates immunogenicity through induction of antibodies to the NANP region of the circumsporozoite protein. This antigen is fused to the hepatitis B surface antigen alongside an adjuvant of AS01. With a global aim to license a vaccine with 75% efficacy by 2030, RTS,S is unlikely to be sufficient alone. Another pre-erythrocytic protein-in-adjuvant malaria vaccine, which also incorporates hepatitis B surface antigen and circumsporozoite protein, is R21. R21 has recently shown efficacy exceeding WHO targets in phase 2b trials in Burkina Faso.[2] This vaccine uses the adjuvant Matrix-M, similar to the NVX-CoV2373 COVID-19 vaccine that also uses a recombinant protein with Matrix-M. The Com-COV2 results suggest that perhaps a future malaria vaccine regimen might incorporate, for example, RTS,S

as a first dose and an R21 booster. This booster of protein (circumsporozoite protein) in adjuvant (Matrix-M) might optimise immunogenicity responses against circumsporozoite protein.

Heterologous viral vector approaches have long aimed to optimise T-cell responses. Ongoing research interest in adenoviral vectors showed ChAd63-modified vaccinia virus Ankara with ME-TRAP antigen induced polyfunctional T-cell activity of high magnitude.[3] T-cell immunity is a significant correlate of protection for malaria, and insufficient cellular immunogenicity might limit efficacy and durability of vaccine candidates. In murine models, adoptive transfer of MHC-activated CD8+ T cells targeting Plasmodium selectively reduced hepatocyte parasitic burden.[4] For the RTS,S vaccine, several epitopes have been matched to CD4+ cell responses.[5] Indeed, the magnitude of T-cell ELISPOT responses after viral vector-based immunisation strategies has been correlated with malaria protection and presence of memory cell population at 6 months post-sporozoite challenge.[6] Heterologous adenoviral vaccination regimens have been widely used with the rollout of the Sputnik V COVID-19 vaccine, using adenovirus 26 and adenovirus 5 vectors.[7] Our understanding of adenoviral vaccines has markedly improved through their licensing during the COVID-19 pandemic. The combination of a viral vector and protein-in-adjuvant has been trialled in malaria, including a range of antigens in addition to differing platforms. The combination of RTS,S (based on circumsporozoite protein) and viral vectors that express an optimised antigen known as ME-TRAP produced high sterile efficacy against parasitic challenge.[8] By using a range of antigens in this approach, heterologous malaria vaccine strategies could incorporate blood-stage antigenic targets to enhance breadth of immunogenicity—eg, using blood-stage antigen RH5 in combination with existing targets, such as circumsporozoite protein.

We have learned from COVID-19 vaccination strategies that a greater interval between first and second dose can enhance immunogenicity, as seen in those who received ChAdOx1 nCoV-19.[9] A phase 3 trial showed delayed administration of even fractional third doses in an RTS,S course can enhance immunogenicity,[10] and so consideration of delayed booster doses alongside heterologous strategies could optimise vaccine strategy.

The Com-COV2 findings provide new insights into enhancing vaccine immunogenicity and suggest that heterologous combination vaccine approaches incorporating Matrix-M boosting could be translated for use in malaria vaccinology to optimise cellular immune responses. Mixed vaccine approaches incorporating recombinant protein, adenoviral, and bloodstream vaccine candidates could pave the way towards the holy grail of malaria vaccine strategy.

Guy's and St Thomas' Foundation Trust has received a grant from Novavax. ALG has been involved in non-commercial leadership of a malaria vaccine trial incorporating Matrix-M (VAC072)—this trial was sponsored by the University of Oxford. ALG has previusly worked at the University of Oxford, which holds the patent on the promotor construct that is often used in ChAdOx1-vectored vaccines. ALG holds no currect affiliation with the University of Oxford, but is names on this patent held in the name of the university. Funds were given to charity in lieu of honoraria for ALG speaking on vaccines. Oxford University has entered a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19. ALG is named as an inventor on a patent covering use of a particular promoter construct that is often used in ChAdOx1-vectored vaccines and is incorporated in the ChAdOx1 nCoV-19 vaccine. ALG might benefit from royalty income paid to the University of Oxford from sales of this vaccine by AstraZeneca and its sublicensees under the University's revenue sharing policy.

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