

Government), and the European Commission, during the conduct of the study, and grants from Sanofi and Roche, unrelated to this Correspondence. MH reports grants from The Belgian Center for Knowledge and Fonds Erasme-COVID-ULB, during the conduct of the study, and personal fees from Gilead, unrelated to this Correspondence. CB reports personal fees from Da Volterra and Mylan Pharmaceuticals, unrelated to this Correspondence. All other authors declare no competing interests. This study received funding from the EU's Horizon 2020 Research and Innovation Programme, Austrian Group Medical Tumor, Belgian Health Care Knowledge Centre, Fonds Erasme-COVID-Université Libre de Bruxelles, Inserm REACTing network, the French Ministry of Health, Paris Ile-de-France Region, European Regional Development Fund, Portugal Ministry of Health, Portugal Agency for Clinical Research and Biomedical Innovation, European Union Commission, and Domaine d'intérêt majeur One Health Ile-de-France. Remdesivir was provided by Gilead free of charge. FM and CB are joint last authors. Members of the DisCoVeRy Study Group are listed in the appendix.

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Is triple artemisinin-based combination therapy necessary for uncomplicated malaria?

We thank Chengchao Xu and colleagues¹ and Charlotte Rasmussen and Pascal Ringwald² for their interest in our studies^{3,4} on triple antimalarial combination therapies (TACTs). TACTs are developed to counter the increasing problem of *Plasmodium falciparum* resistance to artemisinins and their partner drugs in artemisinin combination therapies (ACTs).

Xu and colleagues suggest that rotating ACTs with different partner drugs, adjusting the time course of artemisinin treatments, or exploring improved artemisinin derivatives would be better strategies to counter these resistance problems. Drug rotation is what has been happening already, albeit reactively, but it is operationally challenging. Experience from several countries in southeast Asia suggests that changing first-line antimalarial therapy often takes several years to implement, even when treatment failure rates have risen. Meanwhile, artemisinin resistance facilitates the emergence and selection of partner-drug resistance, jeopardising the small number of available ACT partner drugs. Combining the potent, but short-acting, artemisinin component with two slower, but longer-acting, matching partner drugs in TACTs provides mutual protection against resistance.⁵ The alternative of prolonging the standard 3-day ACT course might improve treatment efficacy but for several ACTs this would require a shift to a second ACT halfway through the treatment course to avoid partner-drug accumulation and toxicity. This more complex treatment regimen would likely compromise treatment adherence. Unfortunately, improved artemisinin derivatives and other new antimalarial compounds are not expected within the next 5 years.

We agree that reducing adverse effects and increasing cost-effectiveness are essential in the development of TACTs. The expected longer therapeutic lifespan of TACTs compared with ACTs will also be a crucial element of this cost-benefit analysis.

Rasmussen and Ringwald state that well matched (triple) combinations might be the future of malaria treatment. Delaying antimalarial drug resistance with TACTs has become an increasingly relevant consideration with the emergence of artemisinin resistance in Africa.⁶ Ideally, a triple combination would include only drugs that are individually curative, and without existing resistance. However, the current reality is a choice between a small number of available antimalarials. Artemether-lumefantrine–amodiaquine was studied because of the well matched pharmacokinetic profiles of the partner drugs and the in-vitro counteracting resistance mechanisms.⁷ In addition, the combination has shown excellent safety and efficacy in areas of highly resistant *falciparum* malaria in the Greater Mekong subregion, in which the number of cases is falling but elimination has not yet been achieved.^{4,5} Artemether-lumefantrine–amodiaquine is now being further evaluated in a large randomised trial in Africa and a fixed-dose combination is in development.

The Mahidol–Oxford Research Unit (MORU) has received funding for other studies of antimalarial treatment from Fosun Pharmaceuticals, which manufactures artemisinin combination therapies. We declare no other competing interests.

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Comparable neutralisation evasion of SARS-CoV-2 omicron subvariants BA.1, BA.2, and BA.3

Published Online
April 12, 2022

[https://doi.org/10.1016/S1473-3099\(22\)00224-9](https://doi.org/10.1016/S1473-3099(22)00224-9)

The SARS-CoV-2 omicron (B.1.1.529) variant has rapidly become globally dominant, displacing the previously dominant delta (B.1.617.2) variant. The viral spike (S) protein is the key target of the neutralising antibody response, and the omicron variant harbours more than 35 mutations in the S protein, which allow highly efficient evasion from neutralising antibodies.¹ In keeping with these findings, the omicron variant efficiently spreads in populations with a high percentage of convalescent or vaccinated individuals.^{2,3}

The three main subvariants of the omicron variant are BA.1, BA.2, and BA.3. Initial data suggest that BA.2 might have a growth advantage over BA.1,⁴ posing a rapidly increasing threat to health systems. The omicron subvariants display remarkable differences regarding

S protein mutations, particularly with respect to the N-terminal domain and the receptor-binding domain (appendix pp 2–3), which are known to harbour key epitopes of neutralising antibodies.^{5,6} Here, we compared BA.1, BA.2, and BA.3 for sensitivity to neutralisation by antibodies induced by infection and vaccination, using pseudoviruses as a model system, which adequately mirrors SARS-CoV-2 neutralisation by antibodies.⁷

We analysed particles harbouring the S protein of B.1—which is identical to the wildtype strain apart from the D614G mutation—and S proteins of BA.1, BA.2, and BA.3. We first examined neutralisation by antibodies from convalescent patients, who were infected during the first (February to May, 2020) and second (December, 2020, to February, 2021) waves of COVID-19 in Germany (appendix pp 2–3, 4–6). Neutralisation of particles bearing the B.1 S protein (B.1_{pp}) was robust, whereas neutralisation of BA.1_{pp} and BA.3_{pp} was at least 32-times less than B.1_{pp} (BA.1 p=0.0020; BA.3 p=0.0020). Neutralisation of BA.2_{pp} was also diminished, but the reduction was less pronounced than that measured for the other omicron subvariants (9.2-times less than B.1_{pp}; p=0.0020).

Analysis of neutralisation by antibodies induced by double vaccination with BNT162b2 (BNT) yielded similar results as neutralisation with antibodies from convalescent patients (appendix pp 2–3). Particles harbouring the S proteins of BA.1 and BA.3 showed 17-times lower neutralisation than B.1_{pp} (BA.1 p=0.0020; BA.3 p=0.0020), whereas neutralisation of BA.2_{pp} was 9-times reduced (p=0.0020). Triple BNT vaccination induced a more potent antibody response, and only modest evasion of neutralisation was seen for particles bearing omicron S proteins (BA.1 2.5-times, p=0.0039; BA.2 1.9-times, p=0.012; BA.3 2.4-times, p=0.0039; appendix pp 2–3). Finally, neutralisation by antibodies induced in fully vaccinated (three vaccine doses)

individuals with breakthrough infection during the fourth wave in Germany (October, 2021, to January, 2022, dominated by the delta variant) was most potent and neutralisation of particles bearing omicron S protein was 9–12-times less efficient than B.1_{pp} (BA.1 p=0.0020; BA.2 p=0.0039; BA.3 p=0.0039; appendix pp 2–3). However, no significant differences were observed between BA.1_{pp}, BA.2_{pp}, and BA.3_{pp} (appendix pp 2–3).

Our results show that all presently circulating omicron subvariants evade neutralisation by vaccine-induced antibodies with comparably high efficiency, suggesting that increased antibody evasion is not the reason for the current expansion of BA.2 in several countries.^{4,8} Since currently available vaccines provided robust protection against early omicron isolates circulating in South Africa from Nov 15 to Dec 7, 2021,³ which was likely to be BA.1, our results suggest that this protection should extend to all omicron subvariants.

SP acknowledges funding from Bundesministerium für Bildung und Forschung (BMBF; grant numbers 01KI2006D, 01KI20328A, 01KX2021), the Ministry for Science and Culture of Lower Saxony (grant numbers 14-76103-184, MWK HZI COVID-19), and the German Research Foundation (DFG; grant numbers PO 716/11-1, PO 716/14-1). MSW received unrestricted funding from Sartorius, Lung research. H-MJ received funding from BMBF (grant numbers 01KI2043, NaFoUniMedCovid19-COVIM 01KX2021), Bavarian State Ministry for Science and the Arts, and DFG through the research training groups RTG1660 and TRR130, the Bayerische Forschungsförderung (Project CORAd), and the Kastner Foundation. GMNB acknowledges funding from the German Center for Infection Research (grant number 80018019238) and a European Regional Development Fund (Defeat Corona, grant number ZW7-8515131, together with AD-J). All other authors declare no competing interests.

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