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.

N gonorrhoeae infections, especially those caused by strains with decreased susceptibility to cephalosporins.[7–9]

Whereas screening strategies for *N gonorrhoeae* and *C trachomatis* often differ, many laboratory-developed and commercial test systems test for both microorganisms automatically. Moreover, current and future platforms can also include additional targets such as *Mycoplasma genitalium* and *Trichomonas vaginalis*.[10] Since a positive test result leaves the clinician little option than providing additional treatment, it should be emphasised that screening should be done rationally, based on the clinical relevance of the infection and the risk profile of the patient. Therefore, laboratories should not report results of tests that have not been ordered, even if they are produced automatically. A positive test result on a microorganism that was not asked for, and of which the clinical importance is highly doubtful, will increase the chance of overtreatment and the induction of antimicrobial resistance in the long run.

We declare no competing interests.

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Emerging evidence on heterologous COVID-19 vaccine schedules—to mix or not to mix?

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As of February 2022, 27 different COVID-19 vaccines have been authorised by one or more regulatory authorities for specific or widespread use.[1] Of these, eight vaccines have received a WHO Emergency Use Listing (EUL).[2] Although homologous vaccination remains standard practice, heterologous schedules that use more than one product in an individual's dosing series offer several potential benefits, including enhanced programmatic flexibility.

We did a comprehensive review of available data on the safety, immunogenicity, and effectiveness of heterologous vaccine schedules (for methods, see appendix pp 1–3). We identified 48 studies that tested a combination of WHO EUL COVID-19 vaccines from different platforms. These included seven controlled trials and 41 observational studies. Schedules involved a combination (in any order) of vectored–mRNA vaccines (36 studies), vectored–inactivated vaccines (eight studies), and inactivated–mRNA vaccines (eight studies). No protein-based vaccines had received a WHO EUL at the time of the review. A total of 37 studies considered heterologous primary schedules (involving more than one product during a two-dose primary series), whereas 13 considered heterologous boosting (among individuals who have previously received a complete homologous primary series). Most studies considered humoral immune response endpoints (38 studies), with a subset reporting on safety (23 studies) and vaccine effectiveness (VE; 11 studies).

See **Online** for appendix

The majority of VE studies (nine of 11) reported on heterologous primary schedules involving ChAdOx1-S followed by an mRNA vaccine (appendix pp 6–8). VE against infection or symptomatic disease following this heterologous regimen (estimates ranging from 61% to 91%) was similar to or marginally greater

than that of homologous ChAdOx1-S (43–89%), and commensurate with that of two mRNA vaccine doses (69–90%). Short-term VE against hospitalisation following heterologous ChAdOx1-S–mRNA was greater than 95% across studies in Canada, Chile, and Spain.[3-5]

Two studies reported on VE following heterologous booster (third) doses. In the UK, administration of BNT162b2 at least 6 months after a primary series of ChAdOx1-S had a VE against symptomatic disease of 93% (95% CI 92–94).[6] This was very similar to the VE of 94% (93–95) observed after a homologous booster dose of BNT162b2 among individuals primed with two doses of BNT162b2. Among individuals in Chile who received a primary series of the inactivated vaccine CoronaVac, heterologous, as opposed to homologous, boosting with ChAdOx1-S or BNT162b2 was associated with an absolute increase of 11–25% in VE against infection, symptomatic disease, hospitalisation, and intensive care unit admission (appendix pp 6–8).[4]

Data on the immunogenicity of heterologous schedules are available for a wider range of vaccine combinations (appendix pp 4–5, 9–14). These findings must be interpreted with caution given the absence of an established correlate of initial or long-term protection. Differences in dosing interval between homologous and heterologous vaccine recipients were also apparent in several of the studies included. Despite these caveats, several consistent trends are emerging. Compared with homologous inactivated vaccine schedules, heterologous schedules have consistently shown enhanced immunogenicity when inactivated vaccines are administered before or after either vectored or mRNA vaccines (appendix p 4). Vectored vaccines have shown enhanced immunogenicity (relative to homologous vectored vaccine schedules) when administered before or after mRNA, but not inactivated vaccines (appendix p 4). By contrast, mRNA vaccines have shown no clear evidence of enhanced immunogenicity (relative to homologous mRNA vaccine schedules) when administered before or after vectored or inactivated vaccines (appendix p 4). Notably, several studies have shown approximate equivalence of the antibody response induced by heterologous vectored–mRNA versus homologous mRNA-only schedules.[7,8]

The order of vaccine products might also be important, albeit apparently less so than the combination. The UK Com-COV study reported somewhat higher antibody concentrations following ChAdOx1-S–BNT162b2 than following BNT162b2–ChAdOx1-S.[9] However, both heterologous groups exhibited higher antibody concentrations than individuals who received two doses of ChAdOx1-S.

A key caveat across the included studies is the small sample size for most heterologous product combinations and the shortage of extensive safety data. Where reported, heterologous schedules have typically shown higher short-term reactogenicity compared with homologous schedules,[10,11] although not all studies have observed this difference.[12] A study in Canada documented higher rates of myocarditis or pericarditis when mRNA-1273 was administered as a heterologous second dose within 30 days of BNT162b2 compared with after mRNA-1273,[13] although it remains to be seen whether this difference will be confirmed by additional studies. Further monitoring for rare adverse events associated with heterologous vaccination is essential. In the interim, product-specific safety profiles can be considered by policy makers contemplating the use of heterologous schedules, albeit with the knowledge that these could be modestly altered in the context of heterologous usage.

Heterologous schedules are poised to play an increasingly important role within the global COVID-19 vaccine strategy. In part, this will be driven by pragmatism as countries contend with variable supply for different vaccine products. However, independent of access considerations, the emerging VE and immunogenicity data highlight the value of heterologous schedules, depending on the platforms involved and the order of products used. A flexible approach to heterologous schedules is warranted as we seek to make optimal use of a diverse vaccine portfolio.

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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