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.

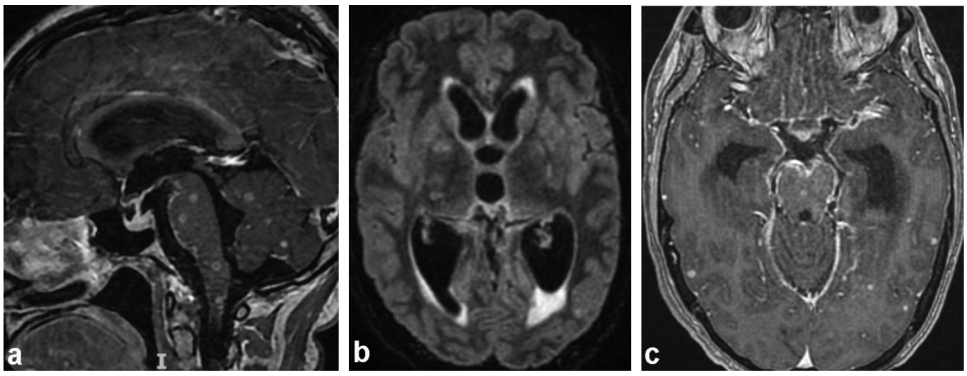

Fig. 1. a. T1 MRI after gadolinium infusion, sagital. Hyperpressure hydrocephalus with fourth ventricular and cisterns dilatations. Note the multiple nodular parenchymatous enhancements. b.T2/FLAIR MRI, axial. Ventricular dilatations involving lateral and third ventricles. c. T1 MRI after gadolinium infusion, axial. Leptomeningeal arachnoïditis and dilatation of the temporal horns of the lateral ventricles.

pathogen load, which is probably less decisive in TBM [5]. Nonetheless, as illustrated by this case, we believe that repeated depletive lumbar punctures might offer a potential benefit for patients presenting with high intracranial pressure or clinical improvement after the initial puncture.

Disclosure of interest

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Mosaic vaccination schedule: An unexpected card to play against SARS-CoV-2?

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Sir,

Logunov et al. recently reported on their phase 3 randomized controlled trial (RCT) of a new COVID-19 vaccine (Gam-COVID-Vac) [1]. As an mRNA-based vaccine, Gam-COVID-Vac targets the glycoprotein S of the SARS-CoV-2 [2,3], and shares significant conceptual points with ChAdOx1 nCoV-19 (AZD1222)[4]. Both vaccines rely on replication-deficient adenoviruses acting as carriers for the target gene, but while ChAdOx1 nCoV-19 is a 2-dose homologous formulate derived from chimpanzee adenoviruses, Gam-COVID-Vac was designed as a heterologous vaccine, based on human recombinant adenoviruses type 5 and 26 [1,4].

Notwithstanding such analogies, reported performances have been strikingly different. As shown in Table 1, with an estimated crude efficacy of 91.64%, the Gam-COVID-Vac outperformed pooled estimates for ChAdOx1 nCoV-19 (i.e. 71.62%), and was found to be directly comparable to mRNA-1273 and mRNA-BNT162b2 vaccines (i.e. 93.03% and 95.08%, respectively) [2,3]. While mRNA-based vaccines require extreme-cold storage conditions, adenovirus-based vaccines, particularly Gam-COVID-Vac, can be stored either in liquid or freeze-dried form, at temperatures (respectively -18 °C and 2-8 °C) that are compatible with a more conventional cold chain. In other words, Gam-COVID-Vac may represent an unexpected but valuable card to play in the global efforts against SARS-CoV-2.

A comparison of available data with the interim report from Voysey et al. [4] on ChAdOx1 nCoV-19 can suggest some tentative explanation for the performances of Gam-COVID-Vac, with potential real-life implications.

Firstly, it should be stressed that the report on ChAdOx1 nCoV-19 included four different trials[4,5]. One of them (i.e. COV002) involved a subgroup with a heterologous schedule; among 1367 participants (36.5% of the total sample) the first shot contained around half of the standard dose (i.e. 2.2×10^{10} viral copies vs. 5×10^{10} viral copies), which was administered as the booster dose.

Table 1
Summary of reports on phase 2/3 trials for COVID-19 vaccines.

Study	Characteristics of vaccine	Dosage	Dose interval	Placebo	Older groups included in the trial	No. of cases	% of older age group	No. of positive cases, %	No. of controls	% of older age group	No. of positive cases, %	Crude Efficacy
Baden et al., 2021[2]	mRNA-1273	100 μg × 2	28 days	Saline	≥ 65 years	14550	24.8%	19, 0.13%	14598	24.7%	269, 1.84%	93.03%
Polack et al., 2020 [3]	mRNA-BNT162b2	30 μg × 2	21 days	Saline	> 55 years	17397	43.1%	8, 0.05%	17498	43.1%	162, 0.93%	95.08%
Voysey et al., 2021 [4]	Replication-deficient chimpanzee adenovirus Ox1	2.2×10^{10} viral particles × 2	4 to 12 weeks	MenACWY	< 55 years	1367	-	3, 0.22%	1374	-	30, 2.18%	90.14%
		5×10^{10} viral particles × 2	28 days	MenACWY	≥ 55 years	2377	21.0%	15, 0.63%	2430	20.9%	38, 1.56%	60.03%
		$3.5–6.5 \times 10^{10}$ viral particles × 2	4 to 12 weeks	MenACWY + saline	≥ 55 years	2063	10.7%	12, 0.58%	2025	9.5%	33, 1.63%	64.68%
Voysey et al., 2021[5]		5×10^{10} viral particles × 2	4 to 12 weeks	Saline	≥ 55 years	1067	N/A	15, 1.41%	1017	N/A	91, 8.95%	85.49%
Logunov et al., 2021 [1]	Replication-deficient human adenoviruses rAd5 rAd26	10^{11} viral particles × 2, first dose rAd26, second dose rAd5	21 days	Vaccine buffer	≥ 50 years	14964	34.2%	16, 0.11%	4902	34.3%	62, 1.26%	91.64%

Notes: crude efficacy was calculated as 1–Odds (OR) × 100, where the OR was calculated as OR = (a/b)/(c/d) = (a × d)/(b × c) where a is the number of vaccinated participants with COVID-19, b is the number of vaccinated participants without COVID-19, c is the number of unvaccinated participants with COVID-19, d is the number of unvaccinated participants without COVID-19. Figure were retrieved from reported studies; where not directly reported, corresponding estimates were reverse-calculated.

With an estimated efficacy of 90.14%, this cohort outperformed the COV002 subgroups treated with the standard doses and a similar schedule (60.02%). However, as this subgroup only included participants less than 55 years old, the generalizability of these results appeared quite difficult.

Secondly, the performances of ChAdOx1 nCoV-19 were influenced by the schedule. Even though it was originally designed for a longer dosing interval (up to 12 weeks) [6], 1459 (53.2%) out of the 2741 participants in the heterologous group of COV002 trial received the second dose at least 12 weeks after the first [4]. In comparison, the COV003 trial–with an interval ranging from 4 to 12 weeks, exhibited an estimated efficacy of 64.68%, while a subanalysis including all participants having received the two doses with an interval ≥ 6 weeks scored 65.14%. Interestingly, in a further trial (COV005) characterized by a longer inter-dose time lapse, crude vaccine efficacy reached 85.49%, with an adjusted estimate of 82.4% in participants having received the second dose at an interval of 12 weeks or more [5,6].

The easiest explanation for these inconsistent results may be linked with the possibly differing representations of older age groups in the different trials. However, in the Gam-COVID-Vac trial, participants aged 50 years or more accounted for around 1/3 of total sample, a share that is comparable to mRNA-based vaccine trials [2,3]. Even though older patients exhibited an increased likelihood of developing SARS-CoV-2 infection when compared to younger patients (i.e. Odds Ratio 2.691, 95%CI 0.955 to 7.486) [1], potential risk remained much lower than that ascertained in non-vaccinated participants (i.e. OR 0.077, 95%CI 0.033 to 0.167, estimated vaccine efficacy of 91.8%). Similarly, ChAdOx1 nCoV-19 efficacy among older subjects was not explicitly reported, but as 5 out of 718 participants aged 55 years or more developed SARS-CoV-2 infection, the risk was quite similar to that in younger age groups (OR 1.178, 95%CI 0.484 to 3.053). In other words, no appreciable age-dependent effect was found for either ChAdOx1 nCoV-19 or Gam-COVID-Vac.

A more subtle explanation may be found in the complex interplay between adenoviral carriers and the immune system. Because of their large size, adenoviruses are suitable carriers for target genes, but they are also able to trigger multiple defense mechanisms aimed at clearing the wild-type pathogen [1,4,7,8]. As the adenovirus-driven activation of the immune system may impair the eventual processing of the target genes (in this case, glycoprotein S), escape strategies have been developed, representing the main divergence between ChAdOx1 nCoV-19 and Gam-COVID-Vac [4].

ChAdOx1 nCoV-19 was deliberately based on a potentially less reactogenic, non-human adenovirus, but neutralizing antibodies are induced after the first vaccination, exhibiting a slight decline only after 4 weeks, before being revamped by the booster dose [8]. In other words, repeated doses of the very same carrier elicit something we would otherwise avoid: an immune response potentially detrimental to the appropriate processing of the SARS-CoV-2 antigens. Better performances of COV005, COV003 and among low-dosage subgroups of COV002 may therefore be explained by the waning response of the immune system against the adenoviral carrier following longer intervals. On the other hand, as Gam-COVID-Vac relies on two different carriers [4,6], the immune response elicited by the first shot has reduced interference with the second shot, as does the processing of SARS-CoV-2 glycoprotein S. Not coincidentally, a report on another human adenovirus-based vaccine (i.e. Ad26.COV2.S Covid-19) hinted at satisfactory performances even after a single shot, with no significant improvement of the immune response after a second shot [9].

In summary, while some stakeholders have proposed emergency vaccination strategies relying on heterologous shots and/or longer dosing intervals to cope with vaccine supply shortages, such an approach may represent something more than a temporary exception to more conventional regimes [10]. On the one hand, available data suggest that a "mosaic schedule" has the potential to significantly improve performances of adenovirus-based vaccines. Interestingly, as mRNA-based formulates do not interfere with adenoviral-driven immunity but aim at the very same target (i.e. glycoprotein S), a mixed schedule of mRNA/adenoviral vaccines may be something more than an emergency measure. On the other hand, a heterologous approach based on formulate availability would obviously relieve the significant burden represented by a massive, whole-population vaccination campaign. This is substantially "uncharted territory" in vaccinology, and the increasing availability of disparate SARS-CoV-2 vaccines should impel public health authorities toward a thoughtful evaluation of a promising opportunity.

Disclosure of interest

The authors declare that they have no competing interest. The facts, conclusions, and opinions stated in the article represent the authors' research, conclusions, and opinions, and are believed to be substantiated, accurate, valid, and reliable. However, as this article includes the results of personal research by the authors and presents correspondingly personal conclusions and opinions, parent employers are not compelled in any way to endorse or share its contents and its potential implications.

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