TO THE EDITOR: The positive antibody response to the messenger RNA (mRNA) vaccine described by Jackson et al. (published online on July 14 at NEJM.org) is a hopeful step toward controlling the Covid-19 pandemic. However, this vaccine and other DNA and RNA vaccines against SARS-CoV-2 continuously stimulate cellular production of the target antigen. A mechanism is required to be able to stop the antigen production after a period of time to avoid the possibility of eventual desensitization, as is seen with allergen immunotherapy. Without such a mechanism, a sustained lack of response may make SARS-CoV-2 infection a lot worse in the long run. It will be important to evaluate this potential before declaring that any DNA or RNA vaccine is safe and efficacious.

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Could R.A. Schachar be employed by Pfizer. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Jackson et al. report the successful results of a trial of the mRNA-1273 vaccine, which induced an impressive IgG antibody response. However, Jackson and colleagues, as well as Heaton, in her editorial corresponding to the article, did not comment on IgA. IgA is a crucial first-line defense in mucosal tissues, and we wonder whether there was any increase in SARS-CoV-2-specific IgA.

The role of vaccine-induced IgA is under discussion for parenteral vaccination against rotavirus. Since SARS-CoV-2 primarily infiltrates mucosal tissue, SARS-CoV-2-specific IgA may be necessary for full protection. Moreover, the lack of IgA may cause unprotected spread of SARS-CoV-2 from nasal mucosal tissue. Chumakov and colleagues discussed the use of oral polio vaccine to ameliorate or prevent Covid-19. In both nasal and intestinal cells, Sungnak et al. detected angiotensin-converting enzyme 2 (ACE2), which is crucial for binding of SARS-CoV-2, and transmembrane serine protease 2 (TMPRSS2), which is crucial for uptake of the virus. Thus, the intestinal and nasal mucosa are ideal targets for SARS-CoV-2 and for vaccination to trigger IgA responses. Studies of an oral vaccine containing attenuated SARS-CoV-2 to stimulate an early protective systemic immune response by the highly effective gut-associated immune system are warranted.

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THE AUTHORS REPLY: We agree with Schachar and Schachar that the interim findings of the phase 1 trial of the mRNA-1273 vaccine against SARS-CoV-2 are promising; these findings provided support for the initiation of the phase 2 and 3 trials that are under way. This vaccine is a lipid nanoparticle–encapsidated, nonreplicating, nucleoside-modified mRNA–based vaccine that, after entering the cell cytoplasm, results in rapid, transient expression of the vaccine antigen. The question regarding the duration of immunity is important, and the phase 1 and 2 trials are designed to follow participants for 1 year after the second vaccination and to obtain samples to characterize humoral and cellular immunologic responses. The phase 3 trial is designed to follow participants for 2 years in order to allow assessment of the durability of protective immunity during that interval.

In reply to Schaefer and colleagues: IgA and IgM responses are exploratory immunologic endpoints in the phase 1 trial, and reporting of these findings is planned as part of the reporting of the final results. The role of monomeric IgA induced by parenteral vaccines is unknown, and monomeric IgA is unlikely to reach the mucosal compartment in substantial quantities. Mucosal delivery of vaccine would be needed to reliably induce secretory IgA localized in mucosal tissues. In a study of SARS-CoV-2 infection and the use of mRNA-1273 in nonhuman primates, intramuscular administration of the vaccine protected the animals against upper- and lower-airway challenge with SARS-CoV-2, and S-specific IgG and IgA were detected in bronchoalveolar-lavage fluid after the challenge. Although these findings may suggest that antibody responses correlate with protection, as noted by Corbett et al., further evaluations, including passive-transfer studies and challenge studies of lower, subprotective vaccine doses in nonhuman primates, are warranted to further elucidate antibody specificities or functions that correlate with protection.

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Since publication of their article, the authors report no further potential conflict of interest.

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