group (23 patients, 11.2%) was higher than that in the no-surgery group (12 patients, 5.8%) at 24 months, representing an excess of 11 patients. If only one of the patients had died within this time frame, the results would no longer be significant, according to an unstratified log-rank test.[4] This assumption is conservative, since approximately 1 of 5 patients in the surgery group died within 24 months. The doubling of the increase in early censoring may be due to postoperative complications that were not accounted for in patients who were lost to follow-up. Some of the measured effect could be a product of the inherent Kaplan–Meier limitations when excessive censoring exists.[3] Further investigation is warranted to elucidate the implications and underlying reasons for excessive censoring in the Descriptive Evaluation of Preoperative Selection Criteria for Operability in Recurrent Ovarian Cancer (DESKTOP) III trial.

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No potential conflict of interest relevant to this letter was reported.

1. Harter P, Sehouli J, Vergote I, et al. Randomized trial of cytoreductive surgery for relapsed ovarian cancer. N Engl J Med 2021;385:2123-31.
2. Templeton AJ, Amir E, Tannock IF. Informative censoring — a neglected cause of bias in oncology trials. Nat Rev Clin Oncol 2020;17:327-8.
3. Gilboa S, Pras Y, Mataraso A, Bomze D, Markel G, Meirson T. Informative censoring of surrogate end-point data in phase 3 oncology trials. Eur J Cancer 2021;153:190-202.
4. Bomze D, Asher N, Hasan Ali O, et al. Survival-inferred fragility index of phase 3 clinical trials evaluating immune checkpoint inhibitors. JAMA Netw Open 2020;3(10):e2017675.

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THE AUTHORS REPLY: The reconstructed patient-level data on overall survival obtained by Meirson et al. do not match the actual data. In our trial, data on 18 of 206 patients in the surgery group (8.7%) and 11 of 201 patients in the no-surgery group (5.5%) were censored for overall survival within the first 24 months. If, as proposed, a surplus in censoring was the consequence of post-surgical complications, one would have expected the difference to appear within the first months after randomization and surgery, but the actual numbers censored and the associated Kaplan–Meier percentages at 3, 6, 12, and 24 months were, respectively, 11 (5.3%), 12 (5.8%), 12 (5.8%), and 18 (9.0%) in the surgery group and 8 (4.0%), 10 (5.0%), 10 (5.0%), and 11 (5.6%) in the no-surgery group. Moreover, among the 18 patients in the surgery group who had censored observations within the first 24 months, only 12 underwent surgery, whereas 6 did not. This makes it unlikely that surgery itself is related to a higher risk of censoring. Therefore, we do not share the apprehension expressed by Meirson et al.

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Anti-idiotype Antibodies in SARS-CoV-2 Infection and Vaccination

TO THE EDITOR: Murphy and Longo (published online on Nov. 24 at NEJM.org)[1] elaborate on the possible role played by anti-idiotype antibodies in the pathogenesis of severe adverse reactions to SARS-CoV-2 infection and vaccination, mentioning only myocarditis and immune-mediated thrombosis and thrombocytopenia.

Neuropilin 1 is the second receptor for SARS-CoV-2; it is recognized by the spike protein of the virus and targeted by the virus early during replication.[2,3] This protein has been so far been neglected with regard to vaccine adverse effects.

Over the past 3 months, I have cared for five patients who have had postvaccine serious adverse events involving the peripheral nerves. Four of the patients had severe peripheral neuropathy

with sensory perception deficits and pain in the limbs; two patients had palsy, with partial recovery after 12 and 8 months. One patient had persistent tinnitus (approximately 50 decibels, 500 Hz) in both ears. All five cases occurred within 24 to 36 hours after the first dose of BNT162b2 (Pfizer–BioNTech) in patients without a history of vaccine reactions or of autoimmune or demyelinating disease. Other surveys[4] and single-case reports[5,6] have corroborated my personal observations.

The possibility that anti-idiotype antibodies or other immune-mediated mechanisms targeting neuropilin 1 may be involved in vaccine-related complications, including neurologic sequelae, should be considered during clinical evaluations and investigated to improve the current vaccines.

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1. Murphy WJ, Longo DL. A possible role for anti-idiotype antibodies in SARS-CoV-2 infection and vaccination. N Engl J Med 2022;386:394-6.
2. Cantuti-Castelvetri L, Ojha R, Pedro LD, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science 2020;370:856-60.
3. Daly JL, Simonetti B, Klein K, et al. Neuropilin-1 is a host factor for SARS-CoV-2 infection. Science 2020;370:861-5.
4. Patone M, Handunnetthi L, Saatci D, et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med 2021;27:2144-53.
5. Luca A, Squillaci R, Terravecchia C, et al. Pure sensitive chronic inflammatory axonal polyneuropathy following Pfizer COVID-19 vaccine. Neurol Sci 2021 November 04 (Epub ahead of print).
6. Waheed W, Carey ME, Tandan SR, Tandan R. Post COVID-19 vaccine small fiber neuropathy. Muscle Nerve 2021;64(1):E1-E2.

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TO THE EDITOR: We had previously[1] developed and tested the hypothesis that Murphy and Longo propose in their article. The authors proposed that the Network Hypothesis of Niels Jerne[2] could explain the formation of anti-idiotype immune responses. We wrote, "[It] is likely that these are anti-idiotypic antibodies . . ." and ". . . issues regarding the response to SARS-CoV-2 can potentially be explained using Jerne's Network Theory of the Immune System . . . ." We showed that the measurable levels of angiotensin-converting–enzyme 2 (ACE2) antibodies that Murphy and Longo speculated may exist are present in 81% of patients who have recovered from Covid-19 and are not present in patients who have not been infected.[1] Murphy and Longo proposed that anti-idiotype responses may affect ACE2 function, leading to the induction of inflammatory cytokines. We showed that patients with ACE2 antibodies have reduced ACE2 activity and wrote, "This provides a potential mechanism for alteration of the balance of angiotensin peptides leading to increased Ang II and activation of the immune system." To our knowledge, we were the first to propose and test this hypothesis.

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1. Arthur JM, Forrest JC, Boehme KW, et al. Development of ACE2 autoantibodies after SARS-CoV-2 infection. PLoS One 2021;16(9):e0257016.
2. Jerne NK. Towards a network theory of the immune system. Ann Immunol (Paris) 1974;125C:373-89.

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THE AUTHORS REPLY: De Maria writes about potential anti-idiotype immune responses directed against other targets of the SARS-CoV-2 spike protein, such as neuropilin 1, which could also contribute to off-target effects. We agree that anything the spike protein can bind can therefore also be a target for mirror-image anti-idiotype antibodies and may affect cellular functions. The need for additional basic research on SARS-CoV-2 virus–host interactions is again highlighted. Given the complex and already diverse effects of ACE2 on multiple cell types and pathways, as well as the fact that anti-idiotype antibodies can also be diverse in their effects — in that they can be antagonistic and agonistic and can potentially cause immune-cell attack — further assessment of all potential target molecules is needed.

Harville and Arthur point out that their study, published in September 2021, showed the presence of anti-idiotype antibodies to ACE2 in patients after SARS-CoV-2 infection.[1] Our article was submitted months before their study was published, and we were thus unaware of it. We are heartened by their data, since it supports the idea that anti-idiotype antibodies occur after SARS-CoV-2 infection and may have effects on ACE2 function. However, whether similar anti-

idiotype responses and effects occur after SARS-CoV-2 vaccination still needs to be determined. Since the release of our commentary, we have received correspondence from both patients and clinicians describing evidence of potential autoantibodies to ACE2 in association with protracted adverse events after vaccination. Much more attention to these adverse effects of infection and vaccination, as well as an understanding of the immunologic mechanisms underlying them, is needed.

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The Future of SARS-CoV-2 Vaccination

TO THE EDITOR: We agree with the statement by Monto in his Perspective article (Nov. 11 issue)[1] that immunity to SARS-CoV-2 is waning. However, we think it is not yet clear whether antigenic variation is the main reason why antibodies may lose neutralization potency. This theory is frequently emphasized in the literature, primarily on the basis of convincing data showing that emerging SARS-CoV-2 variants have spike-protein mutations that preclude recognition by certain monoclonal antibodies.[2,3] However, that is not the case for serum samples[4] indicating that SARS-CoV-2 has not generated new serotypes. SARS-CoV-2 is specializing by increasing the affinity of the spike protein to its receptor, angiotensin-converting enzyme 2 (ACE2).[3] In addition to the well-known increases in infectivity and transmission, we have found another important consequence: neutralizing antibodies and serum samples have reduced capability to block spike–ACE2 binding because they are outcompeted by the increasing affinity of the virus for ACE2, providing an "affinity escape" in contrast with a serotype escape.[4] Therefore, only high-affinity antibody and high-affinity serum samples are capable of neutralizing SARS-CoV-2 variants with high ACE2 affinity, such as the delta variant. Consequently, we should optimize vaccines not only by considering antigenic variation[5] but also by increasing the affinity of antibody responses.

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Drs. Bachmann and Mohsen report owning shares in and receiving salaries from Saiba. No other potential conflict of interest relevant to this letter was reported.

1. Monto AS. The future of SARS-CoV-2 vaccination — lessons from influenza. N Engl J Med 2021;385:1825-7.
2. Hastie KM, Li H, Bedinger D, et al. Defining variant-resistant epitopes targeted by SARS-CoV-2 antibodies: a global consortium study. Science 2021;374:472-8.
3. Cai Y, Zhang J, Xiao T, et al. Structural basis for enhanced infectivity and immune evasion of SARS-CoV-2 variants. Science 2021;373:642-8.
4. Augusto G, Mohsen MO, Zinkhan S, Liu X, Vogel M, Bachmann MF. In vitro data suggest that Indian delta variant B.1.617 of SARS-CoV-2 escapes neutralization by both receptor affinity and immune evasion. Allergy 2022;77:111-7.
5. Choi A, Koch M, Wu K, et al. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. Nat Med 2021;27:2025-31.

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THE AUTHOR REPLIES: The data in the letter from Bachmann et al. indicate, as has been reported elsewhere, that the factors producing a reduction in vaccine efficacy against SARS-CoV-2 are complex.[1,2] This point actually complements the main points that I made: this virus is not going away, it will change over time, and updated revaccination of some kind will be necessary at intervals to be determined. Indeed, the emergence of the omicron variant has proved the point somewhat sooner than most experts expected.

We are still in a period of emergency response. Unfortunately, emergencies consume resources; attention spans are not unlimited and detract from long-term planning, which should involve research questions and logistical issues. I proposed influenza vaccination as an example of how the world has addressed a continuing threat. That is not to say that the current structure is ideal; if it were, we would be further along the path to influenza vaccines that provide longer-lasting and broader protection.[3] The point is that we need to start thinking about such questions with regard to Covid-19 vaccines even as we respond to pressing emergencies.