None of the 17 patients met our criteria for rescue intervention. After a median of 6.4 years (range, 2.7 to 9.8), no recurrences or other complications had been identified in these 17 patients.

Of the 11 patients who received an active intervention, 10 underwent craniotomy for excision of the lesion, 2 received adjuvant chemotherapy, 1 received intralesional glucocorticoids, and 6 underwent cranioplasty after craniotomy. One of these patients was initially part of the observation group and had partial regression of the scalp lesion on MRI but underwent surgical resection of the lesion 62 days after diagnosis at the family's request. All 10 patients who underwent surgery had LCH confirmed histologically.

This study supplements retrospective case series with a prospectively collected series by showing the spontaneous resolution of solitary calvarial LCH in children and adolescents. Limitations of this study are that there was no biopsy confirmation of the diagnosis in the 17 patients in the observation group and that alternative diagnoses such as neoplasm could not be ruled out. All the patients whose LCH was managed by observation had a reduction in the size of the scalp lesion by 2 months after study entry, with 15 having complete resolution at 1 year, findings that indicate a likely diagnosis of LCH. Concerns about alternative diagnoses were addressed with the use of a protocol for rescue intervention. The diagnosis of LCH was confirmed on biopsy in all the patients who underwent surgery; these patients had clinical and imaging findings that were similar to those in patients in the observation group.

In this study, the resolution of solitary calvarial LCH after observation alone avoided the risks associated with invasive treatments, particularly surgery. On the basis of this study, we can make no conclusions with respect to recurrence beyond the period of observation of approximately 6 years in these patients.

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Protection against SARS-CoV-2 after Vaccination and Previous Infection

TO THE EDITOR: In previously uninfected participants in the SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study, Hall et al. (March 31 issue)[1] report reduced protection from SARS-CoV-2 infection after 6 months following the receipt of two vaccine doses. Among unvaccinated participants, those with natural infection-acquired immunity had an 81 to 89% lower risk of infection for up to 1 year after infection than those who were previously uninfected. Infection-acquired immunity then waned in unvaccinated participants, but protection remained higher than 90% in subsequently vaccinated persons.

The authors note that sustained infection-acquired protection in their cohort was possibly affected by repeated occupational exposure to Covid-19. However, one mechanism of potentially paramount importance in explaining their finding of greater protection associated with infection-acquired immunity alone than with vaccine-acquired immunity alone is missing from their discussion: the distinct immunization routes

followed by natural infection (airway mucosal route) as compared with intramuscular vaccination (systemic route). There is now evidence that critical components of the mucosal immunity network play a key role in fighting SARS-CoV-2 infection,[2-5] including secretory immunoglobulin A and tissue-resident memory cells (elements of local adaptive immunity) and mucosa-associated invariant T cells, mucosal complement activation, and mucosal interferons (elements of local innate immunity).

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THE AUTHORS AND A COLLEAGUE REPLY: We agree with Matuchansky that mucosal immunity is an important area for further study, particularly in investigating the differences between infection-acquired and vaccine-acquired protection against SARS-CoV-2 infection. We are examining this in a nested cohort of participants in the SIREN study who are coenrolled in the PITCH (Protective Immunity from T Cells in Healthcare Workers) Study,[1] which investigates cellular immune responses and mucosal immunity.

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Ivosidenib and Azacitidine in *IDH1*-Mutated AML

TO THE EDITOR: In the AGILE trial, Montesinos et al. (April 21 issue)[1] found a significant overall survival benefit of ivosidenib–azacitidine over azacitidine monotherapy in patients with *IDH1*-mutated acute myeloid leukemia (AML) who were ineligible for induction chemotherapy. Clinical decision making in this scenario requires a comparison between ivosidenib–azacitidine and venetoclax-based schemes.

Adjusted indirect comparisons that involve pooled populations are methodologically objectionable. Subgroup analyses have an increased probability of alpha and beta errors.[2] Thus, we conducted adjusted indirect comparisons (Bucher's method[3]) with pooled data[4] and subgroup trial results[5] for venetoclax–azacitidine as compared with ivosidenib–azacitidine in patients with previously untreated *IDH1*-mutated AML. We found no significant differences between treatments in adjusted indirect comparisons of overall survival, either in pooled data (hazard ratio for death, 0.43; 95% confidence interval [CI], 0.16 to 1.16) or subgroup trial results (hazard ratio, 0.64; 95% CI, 0.24 to 1.70). The small number of patients who received venetoclax–azacitidine, broad confidence intervals, and low statistical power are limitations.

The use of imprecise adjusted indirect comparisons in clinical decision making should be undertaken with caution. Interesting results obtained with venetoclax–azacitidine should not be completely rejected, but they are less reliable than data on ivosidenib–azacitidine. It seems reasonable to provisionally prefer ivosidenib–azacitidine