

the number of cases and the number of Covid-19–related hospitalizations in health care workers between the unvaccinated period and the period beginning 14 days after the first dose.

Given that vaccination reduces asymptomatic infection with SARS-CoV-2,<sup>2,3</sup> it is plausible that vaccination reduces transmission; however, data from clinical trials and observational studies are lacking.<sup>4,5</sup> We provide empirical evidence suggesting that vaccination may reduce transmission by showing that vaccination of health care workers is associated with a decrease in documented cases of Covid-19 among members of their households. This finding is reassuring for health care workers and their families.

Anoop S.V. Shah, M.D.

London School of Hygiene and Tropical Medicine  
London, United Kingdom

Paul M. McKeigue, Ph.D.

University of Edinburgh  
Edinburgh, United Kingdom

David A. McAllister, M.D.

University of Glasgow  
Glasgow, United Kingdom  
david.mcallister@glasgow.ac.uk

and Others

A complete list of authors is available with the full text of this letter at NEJM.org.

Supported by the British Heart Foundation and Wellcome.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on September 8, 2021, and updated on October 28, 2021, at NEJM.org.

This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Accepted Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is available under a CC-BY-ND license at PMC8451182.

1. Shah ASV, Wood R, Gribben C, et al. Risk of hospital admission with coronavirus disease 2019 in healthcare workers and their households: nationwide linkage cohort study. *BMJ* 2020; 371:m3582.
2. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* 2021;397:881-91.
3. Hall VJ, Foulkes S, Saei A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. *Lancet* 2021;397:1725-35.
4. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021;384:1412-23.
5. Chodick G, Tene L, Patalon T, et al. Assessment of effectiveness of 1 dose of BNT162b2 vaccine for SARS-CoV-2 infection 13 to 24 days after immunization. *JAMA Netw Open* 2021;4(6): e2115985.

DOI: 10.1056/NEJMc2106757

## Rare Skin Reactions after mRNA Vaccination, Similar to Jones–Mote Basophil Responses

**TO THE EDITOR:** In a small group of recipients of messenger RNA (mRNA) vaccines against coronavirus disease 2019 (Covid-19), the occurrence of erythematous and indurated skin reactions has been reported at an average of 8 days after the first or second injection.<sup>1</sup> The identification of such hypersensitivity responses has been a focus of study for many years by researchers investigating various systems. Such reactions to mRNA vaccines strongly resemble the primary first-dose flare and secondary skin-test responses that we reported 45 years ago in volunteers who were injected with foreign proteins<sup>2</sup> (Fig. 1A). At that time, we noted that the studied reactions were similar to those described as Jones–Mote responses (JMR) to rabbit serum proteins by Dr. T. Duckett Jones and a medical student, John Mote, in 1934 in the *Journal*.<sup>3</sup>

In our 1976 case report, the antigen that was used was the copper-carrying (and thus blue)

protein called keyhole limpet hemocyanin (KLH), which is found in a Pacific Ocean marine gastropod. We identified the cutaneous JMR to KLH as a strong example of cutaneous basophil hypersensitivity (CBH).<sup>2</sup> This delayed reaction was caused by a T-cell response that is rich in basophils to remnants of an intradermal skin-test injection of a strong foreign antigen, as described by Ann and Hal Dvorak in 1970<sup>4</sup> (Fig. 1B). Our study volunteers who had these JMR and CBH reactions were 20 White Yale medical students. At the time, I spoke with John Mote, then retired at 82 years of age, who visited us and confirmed that the reactions that we observed could indeed be classified as JMR.

It seems that the rare cutaneous hypersensitivity reactions among recipients of mRNA vaccines are responses to the translated spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). JMR and CBH re-

actions to the KLH protein in our skin-immunized volunteers were highly antigen-specific in vivo T-cell–dependent responses to residual antigen that was left at the local site from the first injection, to which the host had a primary immune T-cell JMR. Then similar reactions were elicited to secondary skin-test exposures. Such reactions also include antigen-specific T-cell proliferation with distinct kinetics, reactions that now are ripe for more modern molecular analysis.

Recognition that responses to the mRNA Covid-19 vaccines resemble JMR and CBH reactions may lead to skin testing in patients and to other related studies to better understand SARS-CoV-2 infections. Perhaps so-called “long Covid” has a similar pathogenesis and could respond to treatments appropriate to JMR and CBH reactions. An example may be the improvement that was seen in patients with long Covid who were treated with combined antihistamines, since the source of histamine may be the basophils.<sup>5</sup>

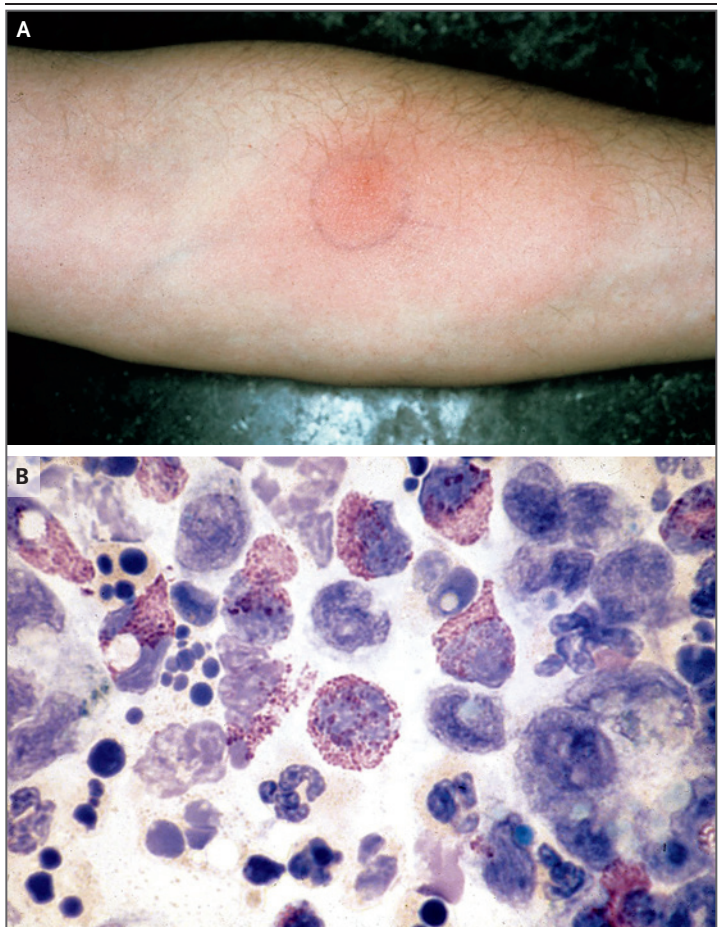
Philip W. Askenase, M.D.

Yale University School of Medicine  
New Haven, CT  
philip.askenase@yale.edu

Disclosure forms provided by the author are available with the full text of this letter at NEJM.org.

1. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed large local reactions to mRNA-1273 vaccine against SARS-CoV-2. *N Engl J Med* 2021;384:1273-7.
2. Askenase PW, Atwood JE. Basophils in tuberculin and “Jones-Mote” delayed reactions of humans. *J Clin Invest* 1976;58:1145-54.
3. Duckett Jones T, Mote JR. The phases of foreign protein sensitization in human beings. *N Engl J Med* 1934;210:120-3.
4. Richerson HB, Dvorak HF, Leskowitz S. Cutaneous basophil hypersensitivity. I. A new look at the Jones-Mote reaction, general characteristics. *J Exp Med* 1970;132:546-57.
5. Glynn P, Tahmasebi N, Gant V, Gupta R. Long COVID following mild SARS-CoV-2 infection: characteristic T cell alterations and response to antihistamines. *J Investig Med* 2021 October 05 (Epub ahead of print).

DOI: 10.1056/NEJMc2111452



**Figure 1. Cutaneous Basophil Hypersensitivity Response after Skin-Test Antigen Injection.**

Shown are the results of a hypersensitivity reaction in a volunteer who received an intradermal skin-test injection of 20  $\mu\text{g}$  of keyhole limpet hemocyanin (KLH) protein 1 week after priming with an intradermal immunization with 222  $\mu\text{g}$  of KLH protein in a 1976 study.<sup>3</sup> Panel A shows the delayed cutaneous erythematous and indurated JMR reaction on day 7 after the second test injection. Panel B shows the results of a Rebeck skin-window examination (in which the top layer of skin is scraped off to facilitate the identification of responding inflammatory cells) after 36 hours. In the numerous basophils that are shown, the cytoplasm is packed with metachromatic purple staining granules that obscure the nucleus. Polymorphonuclear neutrophils and mononuclear cells are also visible.

## CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

**TO THE EDITOR:** Maurer, in his editorial,<sup>1</sup> rightly acclaims the accomplishment of Gillmore et al. (August 5 issue),<sup>2</sup> who used a gene-editing technique that led to reduction of serum transthyretin (TTR) levels in six patients with hereditary

transthyretin amyloidosis (also called ATTR amyloidosis). However, although limiting or abolishing the production of this amyloidogenic precursor protein by hepatocytes could prevent further amyloid deposition, this achievement does not