COVID-19 vaccine side effects: The positives about feeling bad

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Side effects of SARS-CoV-2 vaccines are often troubling but may merely reflect transient production of type I interferons, a normal immune reaction to contact with pathogens.

The development of multiple vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, the cause of coronavirus disease 2019 (COVID-19), within 1 year of the epidemic is unprecedented and an immense accomplishment. The efficacy of many developed vaccines exceeded expectations, and there are high hopes that the epidemic will soon be in the past. Yet, several challenges remain. Vaccinations are far from complete in developed nations and have barely begun in many developing nations, suggesting that achieving worldwide herd immunity against the virus may take several years. There is also the growing problem of vaccine hesitancy, especially in the young who generally cope well with COVID-19, with minimal or even no symptoms. In addition, it is well documented that COVID-19 vaccines can have substantial side effects; indeed, fear of these side effects may approach that of SARS-CoV-2 infection itself in some populations. Therefore, what are the side effects of COVID-19 vaccines—and could they paradoxically be beneficial?

In keeping with their rapid development and production, the mRNA-based vaccines of Pfizer and Moderna have received the most attention with regard to the side effects of vaccination (1, 2). As with other vaccines, these effects can, on rare occasion, be the result of delayed-onset, local allergic reactions. In the vast majority of cases, however, the major complaint is a combination of fever, headache, myalgia, and general malaise, affecting ~60% of recipients after the second dose of the vaccines. These symptoms can be troubling and have been the subject of comment in the press and in top scientific journals. Yet, other than vague reference to an ongoing immune response, the actual cause of the side effects has received almost no attention. So what is the cause of these effects? As discussed here, most of the symptoms can likely be attributed simply to exuberant production of a cytokine that plays a vital role in potentiating early stages of the immune response, namely, type I interferon (IFN-I).

The features and functions of IFN-I have been considered elsewhere (3, 4). In brief, IFN-I comprises a mixture of IFN-α, multiple subtypes of IFN-β, and several other IFNs. IFN-I together with closely related IFN-III (IFN-λ) are produced soon after contact with pathogens and have powerful antiviral effects, acting throughout the body for IFN-I and within the respiratory system for IFN-III. These effects suppress local viral replication and thereby prevent dissemination of virus elsewhere. IFN-I is produced primarily by macrophages and dendritic cells (DC), including both conventional and plasmacytoid DC, and is elicited via interaction with pathogen-associated molecular patterns (PAMPs) expressed by the viral or bacterial pathogen concerned (Fig. 1). PAMPs then interact with complementary pattern recognition receptors (PRRs) expressed by DC, including Toll-like receptors (TLRs) and members of the retinoic acid-inducible gene I (RIG-I)–like receptor family; for mRNA-based vaccines, the PAMP (mRNA) is recognized by multiple PRRs, namely, TLR7, TLR8, and TLR9, RIG-I, and melanoma differentiation-associated protein 5 (MDA5).

The receptor for IFN-I, IFNAR, is expressed by all nucleated cells, and contact with its ligand induces a complex series of intracellular signaling events leading to production of a wide range of cytokines and other mediators that antagonize the pathogen concerned. In particular, early production of IFN-I is crucial for producing an optimal immune response. IFN-I induces activation of DC and thereby enables these cells to present antigen to naïve CD4+ and CD8+ T cells (Fig. 1); activated CD4+ cells then stimulate specific antibody production by B cells, whereas CD8+ cells differentiate into cytolytic...
IFN-1 stimulates synthesis of many different cytokines and chemokines, which of these downstream effects account for the symptoms of IFN-1 administration is still unclear.

The notion that effective immune responses to SARS-CoV-2 and other pathogens are IFN-1 dependent begs the question of how vaccines induce immunity. In addition to T cell receptor recognition of antigen [major histocompatibility complex (MHC)–associated peptides] on DC, T cells need a “second signal” to mount a productive immune response; this signal results from contact of T cell CD28 molecules with CD80 and CD86 molecules on DC. Without such costimulation, the T cell response may lead to tolerance rather than immunity. Hence, a mandatory feature of a successful vaccine is that, in addition to providing a source of antigen, the vaccine must contain an “adjuvant” to induce strong up-regulation of costimulatory molecules on host DC (9). Like IFN-1, adjuvants stimulate DC by binding to PRRs on these cells, which signals the cells to become activated and up-regulate costimulatory molecules. Many components of pathogens have adjuvant activity, notably mRNA and DNA. Moreover, adjuvant activity is conspicuous for Poly(I:C), a synthetic analog of double-stranded RNA; CpG oligodeoxynucleotides, which are short single-stranded synthetic DNA molecules; and Freund’s complete adjuvant, a suspension of dried whole mycobacteria in mineral oil. Notably, these and other nucleic acid–containing molecules can be asymptomatic during SARS-CoV-2 infection. For SARS-CoV-2 infection, it was mentioned earlier that IFN-1 levels are low, perhaps due to the antagonism by the virus. By contrast, IFN-1 production is substantially stronger in females than males and in younger people than the elderly (11). The point to emphasize here is the striking correlation with IFN-1 production. Thus, closely paralleling the intensity of typical immune responses, IFN-1 generation is substantially stronger in females than males and in younger than older people.

For SARS-CoV-2 infection, it was mentioned earlier that IFN-1 levels are low, reflecting antagonism by the virus. By contrast, IFN-1 levels are generally high in influenza infection (3). This difference may explain why “flu-like” symptoms are prominent for influenza but usually mild during SARS-CoV-2 infection. It is worth noting, however, that current COVID-19 vaccines lead to selective expression of just the spike protein, which fails to antagonize IFN-1. Hence, IFN-1 production by the vaccines might be appreciably higher than after SARS-CoV-2 infection itself. Obtaining direct data on this issue is of obvious interest.

In light of the above, the prospect of fatigue and headache after vaccination for COVID-19 should be viewed positively: as a necessary prelude to an effective immune response. The side effects of vaccination will nearly always be mild and transient and indicate merely that the vaccine is doing its job of stimulating production of IFN, the body’s in-built immune stimulator.

**REFERENCES AND NOTES**


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