# COVID-19 and Autoimmunity: Do We Need More Evidence?

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October 9, 2023

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**Dear Editor,**

The ongoing debate revolves around whether autoimmune conditions are triggered or exacerbated by natural SARS-CoV-2 infection or COVID-19 vaccination. Xu *et al* .'s recent investigation has reignited the debate about whether autoimmunity is specifically linked to mRNA vaccines or if non-mRNA vectored vaccines, inactivated virus vaccine, or natural SARS-CoV-2 infection can also trigger autoimmune responses[1]. Xu *et al* . have reported that 25% (3 of 12) of the individuals who received mRNA vaccines (BNT162b2 or mRNA-1273) developed neutralizing anti-type-I interferon antibodies autoantibodies (IFN-I auto-nAbs), while no IFN-I nAbs were observed among individuals (n=8) who received the viral-vectored vaccine (Janssen). While it is an interesting observation, the measures of outcomes are limited by its sample size (n=12 versus n=8) and without any presented hazard ratios. However, there is a substantial body of evidence suggesting that both SARS-CoV-2 natural infection and COVID19 vaccination (mRNA vaccines, vectored-vaccines, and inactivated virus vaccines) are associated with the new onset or exacerbation of existing autoimmune and autoinflammatory conditions[1-9]. I would like to discuss if current evidence is enough to confirm COVID-19 and vaccination as risk factors for autoimmunity or if more evidence is needed.

During the early phase of the COVID-19 pandemic, Bastard et al. reported that approximately 10% (101 out of 987) of individuals with life-threatening COVID-19 pneumonia had IgG IFN-I autoantibodies. The observations by Bastard *et al* . and Xu *et al* . are complementary. Anti-IFN-I autoantibodies could impair the binding of IFN-I to IFNAR1 and IFNAR2, resulting in the inhibition of interferon-stimulated gene (ISGs) transcription[3]. Imperatively administration of mRNA vaccines (Pfizer and Moderna) and vectored vaccines (AstraZeneca) has been linked with post-vaccination emergence of 31 cases of autoimmune conditions, including systemic lupus erythematosus (SLE), thyroiditis, Graves' disease, IgA vasculitis, inflammatory arthritis, dermatomyositis, ulcerative colitis, autoimmune hepatitis, autoimmune hemolytic anemia, autoimmune pancreatitis, ANCA vasculitis, myasthenia gravis, and Sjögren's syndrome (SS). Next, the vectored vaccine Sputnik has also been linked to the emergence of 28 cases of autoimmune conditions in Mexico and Argentina[9].

Alqatri *et al* . reported that autoimmune cases were mostly linked to mRNA vaccines (Pfizer and Moderna). These cases occurred within days to weeks after the administration of the 1st, 2nd, or 3rd doses and were diagnosed using standard laboratory tests[2]. However, Blanco *et al.,* who measured neuronal autoantibodies at 1-, 6-, 9-, and 12-months post-mRNA vaccination, confirm no triggers for autoantibodies or exacerbation of disease among pwMS (n=390) or other inflammatory neurological disorders (n=64). What's the appropriate washout period after SARS-CoV-2 infection and/or COVID-19 vaccination to detect autoantibodies, while avoiding false measurements due to transient autoimmune flares?

Natural SARS-CoV-2 infection is strongly associated with the emergence of autoimmune diseases and the exacerbation of existing diseases, while it has been firmly advocated that the administration of COVID-19 vaccines reduces the risk of autoimmunity[4,7]. In a case-control analysis involving 888463 COVID-19 patients and 2926016 controls, Chang *et al* . identified COVID-19 as a risk factor for several autoimmune conditions, including ankylosing spondylitis, Behçet's disease, celiac disease, dermatopolymyositis, inflammatory bowel disease, mixed connective tissue disease, polymyalgia rheumatica, psoriasis, rheumatoid arthritis (RA), SS, SLE, systemic sclerosis, type 1 diabetes mellitus, and vasculitis[4]. However, receiving a two-dose vaccination of either the mRNA vaccine (Pfizer-BNT162b2) or inactivated virus vaccines (Sinovac-CoronaVac) has been associated with a decreased risk of anti-phospholipid antibody syndrome, Graves' disease, immune-mediated thrombocytopenia, pemphigoid, and SLE[7].

Decoupling antiviral immunity from the onset and exacerbation of autoimmunity is challenging[5]. IFN-I is a disease activity marker for SLE, SS, and RA and is essential for intrinsic antiviral immunity[5,10]. It's an age-associated marker, with anti-IFN autoantibodies observed in patients with specific autoimmune conditions, as well as those who've had SARS-CoV-2 infection or received vaccines. Compared to SARS-CoV-2 infection, synthetic mRNA vaccines involve the controlled presentation of spike S1 protein to the host immune system, while both utilize the host-cell translation machinery.

Intriguing evidence suggests stable autoantibody dynamics following mRNA vaccination, in contrast to COVID-19 patients who show an increased prevalence of new antibody reactivities[4]. Understanding autoimmunity in the context of SARS-CoV-2 variants of concern (VOCs) and the sequence of infection and vaccination introduces additional complexity. However, it's crucial to recognize that in the aftermath of the COVID-19 pandemic, the prevalence of autoimmune conditions has significantly increased. This extends beyond post-acute sequelae of SARS-CoV-2 infection (PASC), and the root cause of vaccine-induced autoimmunity should not be disregarded.

In summary, Xu *et al* . have presented a new line of evidence supporting the hypothesis of vaccine-induced autoimmunity. Therefore, monitoring the long-term effects of COVID-19 vaccines should be conducted on an equal scale as monitoring autoimmunity induced by SARS-CoV-2 infection.

## AUTHOR CONTRIBUTIONS

RSM: Conceptualization and writing the manuscript:

## CONFLICT OF INTEREST STATEMENT

Ranjeet Singh Mahla is an Oxford BMS Fellow.

## DATA AVAILABILITY STATEMENT

No new data generated or analysed.

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