Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

National differences in vaccine hesitancy: a concern for the external validity of vaccine studies

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We read with interest the studies by Renaud Felten and colleagues[1] and Laura Boekel and colleagues[2] published in *The Lancet Rheumatology*, which both contribute essential insights into the perspective of patients with autoimmune and rheumatic diseases on COVID-19 vaccination. The authors reported a moderate willingness (54% [686 of 1266 patients][1] to 61% [1060 of 1727][2]) to be vaccinated against COVID-19 in the two study populations.

One concern about the studies presented by Felten and colleagues and Boekel and colleagues is the lack of focus on national differences in vaccine hesitancy.[3] In Felten and colleagues' international cohort, 320 (25·3%) of 1266 participants were French, whereas all 1727 participants in the cohort of Boekel and colleagues were from the Netherlands. In 2015, French citizens were among the populations with the lowest perception of vaccine safety globally, with 41·0% disagreeing that vaccines are safe.[4] Data from 2019 showed that the perception of vaccine safety varies considerably with nationality. In Denmark, 47·2% of the population strongly agreed that vaccines are safe, compared with only 29·8% of the population in the Netherlands and 29·7% of the French population.[3] Generally, the perception of vaccine safety is more pessimistic in the European and the Western Pacific regions.[4]

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In January, 2021, we did a questionnaire study of 392 Danish patients with systemic lupus erythematosus and rheumatoid arthritis assessing their willingness to be vaccinated against COVID-19. Patient characteristics were as follows: median age 57·5 years (IQR 44·0–67·6), 322 (82·1%) were women, and 200 (51·0%) had systemic lupus erythematosus. In this population, 364 (92·9%) patients wished to be vaccinated, 15 (3·8%) were hesitant, and 13 (3·3%) were unwilling to be vaccinated. The primary concerns expressed by those who were both hesitant and unwilling were fear of short-term (eight [30·8%] of 26 patients) and unknown long-term (12 [46·2%] patients) side-effects, and safety related to the accelerated vaccine development (three [11·5%] patients).

The disparity between the results of the three studies is substantial and presumably due to national differences in vaccine hesitancy and confidence.[3,4] Awareness of these differences is paramount, as they can diminish the external validity of studies addressing vaccine hesitancy in specific patient groups.

WHO named vaccine hesitancy as one of the top ten threats to global health in 2019; they identified complacency, convenience, and lack of confidence as key reasons underlying vaccine hesitancy.[5] We support the conclusion of both studies,[1,2] which is that health-care workers have an essential role in reassuring the community about vaccine safety. However, identifying the cultural backgrounds that underlie the substantial differences between countries in vaccine hesitancy and confidence could prove a meaningful approach when disseminating vaccine information in different nations.

We declare no competing interests. The Danish Rheumatism Association funded the questionnaire study. The funder had no role in data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors contributed equally to study design, data collection, data interpretation, and writing of the report. CA and AT accessed and verified the underlying data.

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Arthritis after SARS-CoV-2 infection

In COVID-19, the pivotal cytokines that provoke severe disease in the lung are similar to those usually targeted by drugs used for treating rheumatoid arthritis. Although COVID-19 is not yet considered as a trigger for rheumatoid arthritis, this similarity has led to the suspicion that COVID-19 might be a risk factor for inducing a rheumatoid arthritis flare.[1] Recently, arthralgia and arthritis have been reported after SARS-CoV-2 infection in three patients that were negative for rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA).[2,3] In this Correspondence, we describe a man who developed arthritis after COVID-19.

On February 20, 2020, a 67-year-old non-smoking man attended a routine clinical check-up at the Shymkent Medical Center for Joint Diseases in Shymkent (Kazakhstan). He did not complain of any joint pain or swelling and testing for RF, which was requested as a routine evaluation, was negative. On May 26, 2020, he developed fever,

anosmia, shortness of breath, and weakness: chest x-rays showed bilateral interstitial pneumonia (appendix p 1) with 83% oxygen saturation. An RT-PCR for SARS-CoV-2 was positive, and the patient was diagnosed with COVID-19. On June 1, 2020, he was admitted to a provisional COVID-19 hospital in Shymkent (Kazakhstan). After 7 days of treatment with ceftriaxone (1 g per day for 4 days), azithromycin (0·5 g per day for 4 days), and non-steroidal anti-inflammatory drugs (three ibuprofen tablets taken per day when necessary), he was discharged from hospital. On July 2, 2020, he developed morning stiffness (>30 min) and symmetric polyarthritis of the knees and hands (appendix p 2). Testing showed a Disease Activity Score of 28 joints with C-reactive protein (DAS28-CRP) of 7·35. Furthermore, a high RF concentration (411 IU/mL, normal range <18 IU/mL), a high erythrocyte sedimentation rate (59 mm/h), and a high concentration of CRP (55 mg/L, normal range <5 mg/L) were reported, but ACPA concentration was low (19·2 U/mL, normal range <20 U/mL). A serological anti-SARS-CoV-2 rapid test (COVID-19 IgG/IgM antibody test; Humasis, Anyang, Korea) was positive for IgG and IgA. A diagnosis of early rheumatoid arthritis was made, and treatment with methotrexate (15 mg per week) and methylprednisolone (8 mg per day) was started. After 1 month, the patient's erythrocyte sedimentation rate was 28 mm/h, and the concentration of CRP was reduced but still high (18 mg/L), with a low joint DAS28-CRP of 2·8. An x-ray did not show any parenchymal lesions (appendix p 1), but a chest CT (appendix p 3) detected residual signs of polysegmental pneumonia in the resolution stage, chronic bronchitis, and emphysema. A quantitative serological SARS-CoV-2 antibody test was negative for IgA (0·1 conventional units) but positive for IgG (13·3 conventional units). ACPA concentration was high (104 U/mL). In October 2020, the patient was still receiving treatment with methotrexate and methylprednisolone, was in remission (DAS28-CRP 2·2), and he returned to work.

The patient survived COVID-19 with a standard treatment approach. An association between COVID-19 and the onset of reactive arthritis has been previously postulated.[2] Approximately 1 month after the resolution of COVID-19 symptoms, the patient developed arthritis with a high RF and, almost 5 months later, a progressive increase of ACPA. However, it is unknown if the persistence of SARS-CoV-2 infection, detected in this patient with the CT via signs of pneumonia in a resolution phase, could have been a factor triggering the onset of arthritis. Moreover, the response to methotrexate and corticosteroids was satisfactory, with remission of joint disease when the patient was still positive for IgG and IgA anti-SARS-CoV-2 antibodies. This case might suggest that SARS-CoV-2 was involved in triggering RF-positive and ACPA-positive arthritis, which might be diagnosed as rheumatoid arthritis, but we cannot rule out the possibility that the onset of this arthritis could have been coincidental. However, previous reports of the presence of autoantibodies after SARS-CoV-2 infection might suggest that this virus might also act as a trigger of arthritis or other autoimmune diseases.[4,5] Long-term observation of patients affected by COVID-19 might provide an answer to this challenging question.

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See **Online** for appendix

COVID-19: angiotensin II in development of lung immunothrombosis and vasculitis mimics

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From a radiological perspective, there is strong evidence that the initial pathological process of COVID-19 lung disease dominantly affects the pulmonary vessels via systemic micro-vascular immunothrombosis, as is supported by pathological reports.[1] We read with considerable interest the recent Viewpoint by Dennis McGonagle and colleagues on COVID-19 vasculitis and vasculitis mimics.[2]

In this Viewpoint, the model presented describing so-called pulmonary intravascular coagulopathy proposes that one of the two broad types of systemic vasculitis described in patients with COVID-19 is mediated by microembolic material that escapes the capillary bed of the lungs and is distributed via systemic arteries to other parts of the body. Importantly, this mechanism assumes the presence of thrombosis within pulmonary vessels on the distal side of the capillary bed, beyond the embolic filtration network of the alveolar capillaries and, thus, the presence of thrombosis in the pulmonary venules of the lung periphery. The model is aligned with growing evidence of the pivotal involvement of pulmonary veins in severe COVID-19, as evidenced by the presence of pulmonary infarcts in the majority of patients at autopsy,[1]