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patients 1 and 2 and from patient 3 himself.

Patient 1 was a 14-year-old boy who presented to the hospital with erythematous-violaceous lesions involving the dorsum of all digits of both feet. After 7 days, a few red macules and papules appeared on the lateral and plantar aspect of both feet and a small ulcer developed on the fifth digit of the left foot (figure). Because a family member had tested positive for SARS-CoV-2, the patient underwent nasopharyngeal swab and was found positive for SARS-CoV-2 on RT-PCR. The lesions disappeared in the following 7 days.

Patient 2 was a 14-year-old boy with no known contact with COVID-19 cases who had been asymptomatic since the beginning of the skin disease, for which his parents requested a teledermatology consultation. Manifestations consisted of small erythematous-violaceous lesions on the dorsum of almost all digits of the feet, some of which were characterised by necrotic aspects with blackish crusts (appendix). The lesions lasted 20 days, with complete healing. Nasopharyngeal swab taken by the family's paediatrician 2 days after the skin manifestations appeared was positive for SARS-CoV-2.

Patient 3 was an 18-year-old boy whose grandfather had COVID-19 pneumonia. After 2 days with fever (38·5°C), the boy reported the appearance of chilblain-like lesions involving the distal part of all digits of the feet (appendix). Skin manifestations remained unchanged for 10 days, suddenly disappearing without treatment. Nasopharyngeal swab taken 4 days after the skin manifestations appeared was positive. The patient was otherwise asymptomatic.

Acute acro-ischaemic manifestations along the course of SARS-CoV-2 infection seem to be different from classic acrocyanosis, erythema pernio, and vasculitis; however, they could represent a cutaneous expression of the typical thrombotic pattern of COVID-19 due to hyperinflammation[4] and altered coagulation and endothelial damage.[5]

During this time, children and adolescents with chilblain-like lesions who are otherwise asymptomatic should undergo SARS-CoV-2 testing, which could help early detection of silent carriers.

We declare no competing interests.

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Prevention of the cytokine storm in COVID-19

The Comment by Marc Feldman and colleagues,[1] published recently in *The Lancet*, discussed the potential of anti-tumor necrosis factor (TNF) therapy to inhibit development of a cytokine storm in patients with coronavirus disease 2019 (COVID-19). Following this Comment, I write to propose that the opioid, meptazinol, might be a possible alternative or addition to anti-TNF therapy, particularly in the UK, where meptazinol is a licensed drug (current licenced supplier Almirall, Barcelona, Spain) and thus could be easily prescribed.

The basis of this suggestion is a study I led with Bayu Teklu and colleagues,[2] in which we studied the Jarisch-Herxheimer (JH) reaction in louse-borne relapsing fever. The JH reaction appeared to be a transient manifestation of a cytokine storm, induced by treatment of relapsing fever with antibiotics, and only lasting for around 2 h after a single curative injection of tetracycline.[3] Notably, concentrations of interleukins 6 and 8 and TNF are increased during this reaction. Meptazinol, an opioid antagonist–agonist or sometimes termed a partial opioid agonist, but not naloxone, supressed the JH reaction,[2] similar to the effect of anti-TNF.[4] Meptazinol reduced high temperature, pulse rate, and breathing rate during the JH reaction. An effect of the JH reaction is exacerbation of any local lesions (in this case, the lungs). The theoretical basis of the action of opioid antagonists was elucidated in an animal model of relapsing fever and described in detail previously.[5] However, a disadvantage of meptazinol is that it is short acting (half-life of about 2 h) and causes nausea and occasional vomiting.

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A trial of meptazinol for COVID-19 in patients presenting with a cytokine storm and in those without, to provide proof of effectiveness, might indicate its efficacy in ameliorating symptoms. The results of such a trial might prove especially useful, given that antipyretics, such as paracetamol and aspirin, have become less favoured by clinicians. Building on this approach, a range of opioids should be tested, particularly in the context of the COVID-19 cytokine storm, to establish if a longer acting and more palatable opioid than meptazinol

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can be used (eg, buprenorphine, half-life 24 h) or even synthesised.

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Tale of three seeding patterns of SARS-CoV-2 in Saudi Arabia

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Human mobility patterns are determinants of disease transmission. This is particularly relevant for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission in Saudi Arabia (population 34 million), which experiences three types of population movements. First is the international and domestic movement of pilgrims in Saudi Arabia. On average each month about 1 million incoming pilgrims from 180 countries merge with about 1 million Saudi-national Sunni pilgrims (75% of the Saudi population) in Saudi Arabia's two holy sites and the nearest entry port of Jeddah.[1] Second is the returning Shiite Saudi-national pilgrims (4·9 million Shiite population in Saudi Arabia) who travel to Iran and Iraq for pilgrimage. Men and women older than 60 years are overrepresented among pilgrims. Third is routine travel to and from Saudi Arabia by Saudis, permanent residents, and non-pilgrim visitors for commerce and tourism, estimated to be about 3 million people each month.

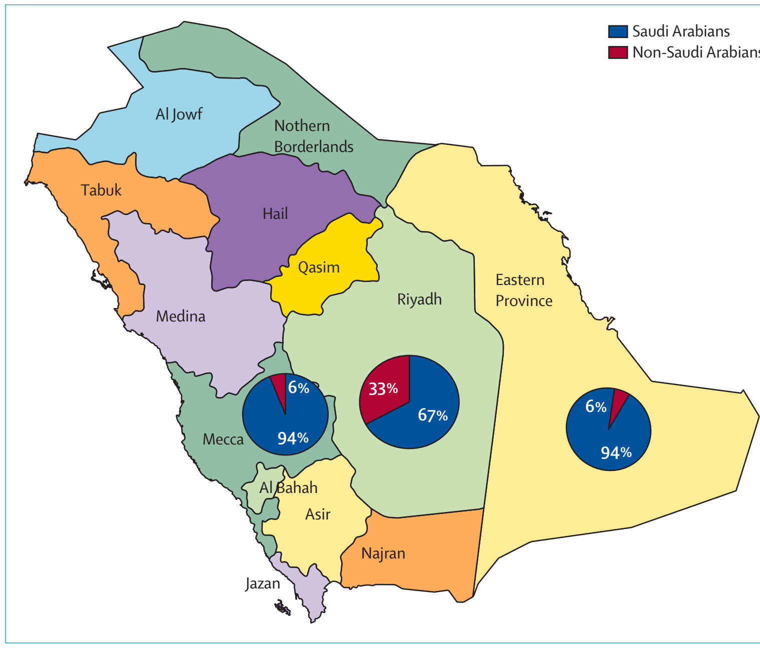

Figure: **COVID-19 distribution in Saudi Arabia on March 15, 2020, by nationality**
COVID-19=coronavirus disease 2019.

We observed three outbreak seeding patterns in Saudi Arabia in the early phase of the coronavirus disease 2019 (COVID-19) epidemic that match the three types of population movements (figure). First, transmission related to international pilgrims in holy sites in Mecca and Medina region, largely among the non-Saudi population (49 [94%] of 52 cases). Second, transmission among returning Saudi Shiite pilgrims in the eastern province, affecting mostly Saudi citizens (45 [94%] of 48 cases). Third, general non-specific spread by routine international travel in the political and diplomatic hub of Riyadh province, mostly among the Saudi population (12 [67%] of 18 cases). The remaining provinces of Saudi Arabia did not have COVID-19 cases in the early phase. Of the three seeding patterns, by April 2, 2020, the second had the greatest affect on accelerating domestic transmission in Saudi Arabia, with highest acceleration of cases seen in the eastern region (99 cases per 100 000). Per 100 000 population, Mecca and Riyadh had 17 cases and eight cases, respectively, on April 2.

Saudi Arabia's ten quarantined student evacuees from China were reported on Feb 16 to have tested negative for SARS-CoV-2.[2] The country's suspension of pilgrimage visas for international visitors on Feb 27 and for all people by March 4 probably helped delay detection of the first case in the Mecca region until March 10. Saudi Arabia implemented comprehensive pandemic mitigation efforts[3] incrementally during March 8–21.

In the early phase of the epidemic, the high proportion of COVID-19 diagnoses in the Riyadh region that were among Saudi nationals (67%) might have resulted from entry restrictions on non-Saudi people and increases in returning Saudi citizens who might have been exposed overseas. The outbreak in the eastern region was reported on March 10 among four returning Saudi pilgrims. Saudi Arabia had not recognised