School of Medicine, Experimental Medicine Building, Yunnan Garden Campus, Nanyang Technological University, 59 Nanyang Drive, 636921, Singapore; [4]Translational and Clinical Research Institute, Newcastle University, Centre for Life, Newcastle upon Tyne, NE1 7RU, UK; and [5]Bristol Dermatology Centre, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
Correspondence: Neil Rajan.
Email: neil.rajan@newcastle.ac.uk

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Oral ivermectin for a scabies outbreak in a long-term care facility: potential value in preventing COVID-19 and associated mortality

DEAR EDITOR, To date, the COVID-19 pandemic has affected over 85 million persons worldwide, with 14% of cases severe and 5% critical, and a general population case-fatality rate of 1%. Age is the main risk factor for severe disease and death,[1] making residents of long-term care facilities (LTCFs) particularly vulnerable.[2] Therapeutic agents for COVID-19 remain sparse, but ivermectin, an antiparasitic, has shown anti-SARS-CoV-2 activity in vitro.[3] Moxidectin, another macrocyclic lactone, with a longer plasma half-life, could also be considered.[4]

On 6 March 2020, a 66-year-old woman (Resident 1) with numerous comorbidities, from LTCF-A (Seine-et-Marne county, in suburban Paris, France) was referred to our dermatology department with profuse scabies. She was treated in our randomized controlled trial (NCT02841215) with ivermectin 400 or 200 µg kg^{-1} (exact dose double-blinded) on days 0, 7 and 14. LTCF-A identified three more residents with scabies, residing on different floors, and declared an outbreak. They were treated accordingly, and all remaining LTCF-A residents and staff (n = 117) were also treated simultaneously with ivermectin (200 µg kg^{-1}, days 0–7, starting 10 March 2020) (Figure 1).

All confirmed or suspected cases of COVID-19 among LTCF-A's residents and staff from 5 March to 15 May 2020 were identified. LTCF-A residents' demographics (age and sex) and COVID-19 clinical outcomes (recovery, hospitalization or death) were recorded. During the same period (5 April to 1 May 2020; no prior data available), all confirmed COVID-19 cases and deaths in all other LCTFs in Seine-et-Marne were systematically declared in the French national online database (https://signalement.social-sante.gouv.fr) and all data were gathered by the Agence Régionale de Santé–Ile-de-France (https://www.iledefrance.ars.sante.fr).

We selected all county-wide LTCFs comparable with LTCF-A in terms of fees and size (50–90 residents). All remaining LTCFs provided aggregated demographic data (age and sex). Each retained LTCF – except LTCF-A – was considered a cluster. R software (v6.1.2; R Foundation, Vienna, Austria) was used to estimate COVID-19 infection and mortality rates, and their distributions. In parallel, an in vitro virological study measured the anti-SARS-CoV-2 activity of ivermectin and moxidectin on VeroE6-monkey kidney cells at increasing concentrations (range 0·05–10 µmol L^{-1}) by RNA quantification and immunofluorescence (with cell viability controlled at each step). We also performed a time-of-drug-addition assay.

Between 5 March and 15 May 2020, 69 LTCF-A residents (median age 90 years, interquartile range 84–94; 78% female) and 52 staff members received ivermectin (Figure 1). Eleven persons presented confirmed or suspected COVID-19 (1·4% declared in the ARS online database), with the first symptoms noticed on 11 March 2020 (Resident 1 on 19 March 2020). One resident (Resident 1) had a SARS-CoV-2-positive reverse-transcriptase polymerase chain reaction. No hospitalizations and no deaths were noted. Forty-five 'matched' county-wide LTCFs were included as a reference sample (out of 177), housing 3062 residents (median age 86 years, interquartile range 87–89; 77·3% female). Among them, a mean of 22·6% (95% confidence interval 16·3–28·9) acquired declared COVID-19, with a lethality of 4·9% (95% confidence interval 3·2–6·5).
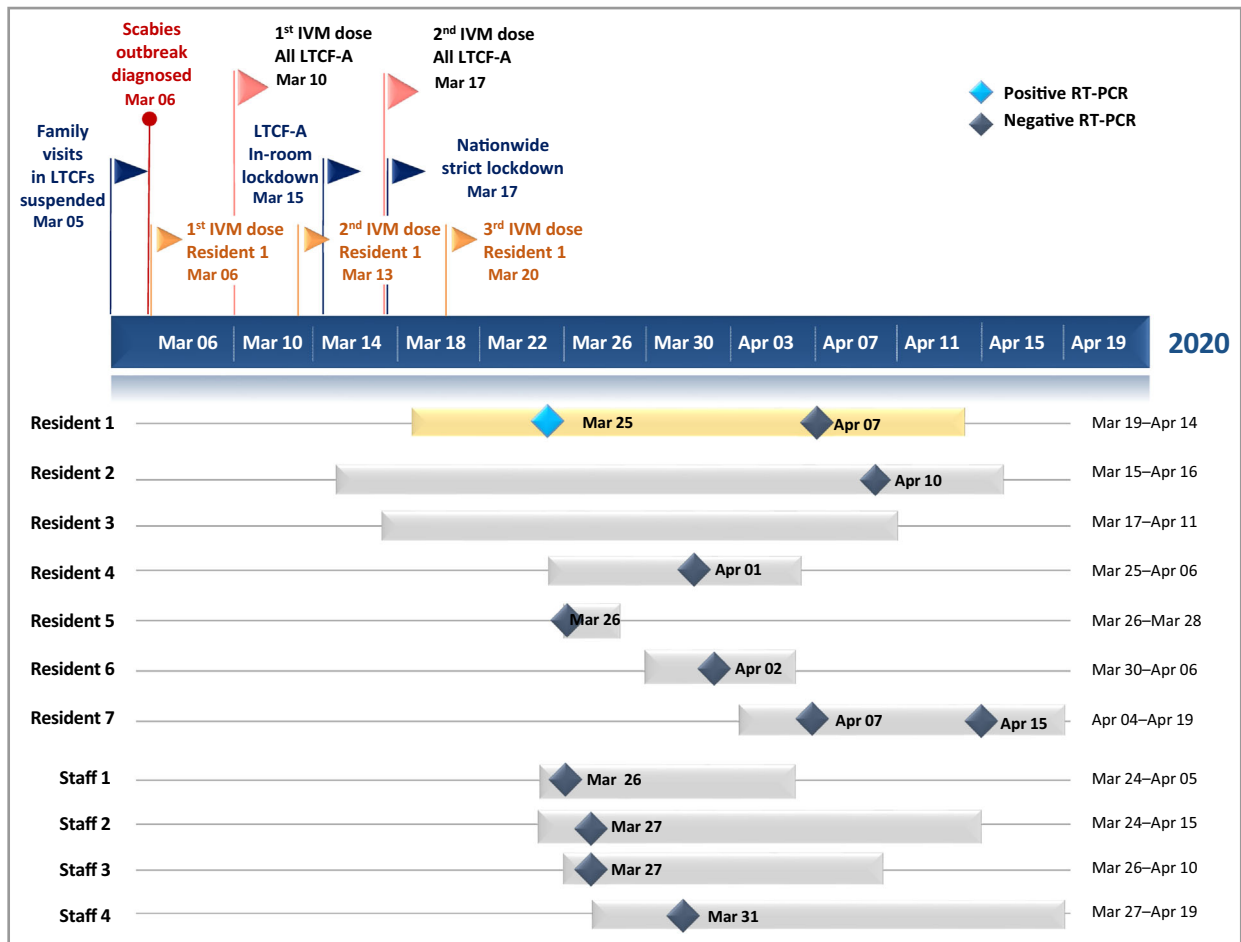
Figure 1 Concomitant COVID-19 and ivermectin-treated scabies outbreak in a long-term care facility. The navy blue timeline represents COVID-19-dictated closure coinciding with onset of a scabies outbreak in long-term care facility A (LTCF-A), and the oral ivermectin (IVM) treatments for the scabies-infested patients (n = 4) and their contacts (n = 117), for a total of 121 IVM-treated individuals, according to NCT02841215 and current therapeutic recommendations on scabies. The bars below the timeline represent the different individuals with confirmed or suspected COVID-19 (LTCF-A residents and staff). Real-time reverse-transcriptase polymerase chain reaction (RT-PCR) (RdRp gene, CT 36 and N gene, CT 34) detected Resident 1's COVID-19 (yellow bar).

The virological study confirmed important *in vitro* antiviral activity, with EC_{50} values of 0.14 ± 0.02 µmol L^{-1} and 0.48 ± 0.08 µmol L^{-1} for ivermectin and moxidectin, respectively. The maximum inhibitions at 5 µmol L^{-1} were 55 000 and 19 000-fold, respectively, without affecting cell viability. The study also showed dose-dependently limited numbers of SARS-CoV-2-infected cells, and complete inhibition of SARS-CoV-2 infection at 2.5 µmol L^{-1}. When ivermectin and moxidectin were added 3 h after infection (i.e. early during SARS-CoV-2 infection), no antiviral effect was seen (data not shown).

To control scabies, the entire LTCF-A population was given ivermectin, while at the same time a COVID-19 outbreak was declared. No ivermectin-exposed LTCF-A resident developed severe COVID-19 or died, while residents from control LTCFs showed higher COVID-19 rates. Usually, once COVID-19 enters an LTCF – in any healthcare system – its rapid dissemination[5] is associated with a high risk of death. Ivermectin is

an antiparasitic drug that is used to treat neglected tropical diseases such as onchocerciasis, helminthiases and scabies, and is evaluated at high doses for malaria control. It could have a protective role in COVID-19 within a therapeutic margin,[6] as supported by our optimized virological study. Other populations might have already benefited from ivermectin, as its use was associated with lower in-hospital mortality in a multihospital retrospective cohort study of 280 North American patients [ivermectin, n = 173 (15%) vs. no ivermectin, n = 107 (25.2%), odds ratio 0.52, 95% confidence interval 0.29–0.96; P = 0.03].[7] There are both epidemiological (i.e. the ecological nature of the data with probability of unmeasured confounding) and virological limitations of the available data, and difficulties in extrapolating *in vitro* antiviral effects against different coronaviruses to clinical efficacy. However, the plausibility is sufficient to carry out further studies to elucidate whether ivermectin (and moxidectin) is or is not an appropriate candidate for the prevention of COVID-19.

C. Bernigaud (iD),[1,2] D. Guillemot,[3,4,5] A. Ahmed-Belkacem,[6] L. Grimaldi-Bensouda,[3,4] A. Lespine,[7] F. Berry,[6] L. Softic,[6] C. Chenost,[8] G. Do-Pham,[9] B. Giraudeau,[10] S. Fourati[1,6] and O. Chosidow (iD)[1,2]

[1]APHP, Hôpital Henri-Mondor, Université Paris-Est, Créteil, France; [2]Research Group Dynamic, Université Paris-Est Créteil, Créteil, France; [3]Université Paris-Saclay, Montigny-Le-Bretonneux, France; [4]APHP, Paris-Saclay, Le Kremlin-Bicêtre, France; [5]Institut Pasteur, Epidemiology and Modelling of Antibiotic Evasion, Paris, France; [6]Inserm U955, Université de Santé, Paris-Est, Créteil, France; [7]INTHERES, Université de Toulouse, Toulouse, France; [8]Long-Term Care Facility Chief Medical Officer, Seine-et-Marne, France; [9]Service de Médecine Interne, Centre Intercommunal de Créteil, Créteil, France; and [10]UMR SPHERE Inserm U1246, Université de Tours, Tours, France
Email: charlotte.bernigaud@aphp.fr

D.G. and A.A.-B. contributed equally. L.G-B. and A.L. contributed equally. B.G. and S.F. contributed equally.

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Linear and disseminated porokeratosis in one family showing identical and independent second hits in *MVD* among skin lesions, respectively: a proof-of-concept study

DEAR EDITOR, Porokeratosis is an autosomal dominant skin disorder characterized by annular or circular skin lesions surrounded by a hyperkeratotic rim called 'cornoid lamella'.[1] Clinical subtypes of porokeratosis have been classified mostly based on age at onset, and the distribution and size of skin lesions.[1] It has been demonstrated that most patients with porokeratosis have a heterozygous germline mutation in genes that encode enzymes of the mevalonate pathway (*MVK*, *MVD*, *PMVK* or *FDPS*) in both familial and sporadic cases.[2,3] Recent reports have claimed that second-hit genetic changes that render the monoallelic mutation biallelic initiate the formation of skin lesions in linear porokeratosis (LP)[4,5] and disseminated superficial actinic porokeratosis (DSAP).[5] Here, we present a familial case of porokeratosis with DSAP in a father and LP in his daughter. Biopsy of multiple skin lesions revealed independent second hits in DSAP, and an identical hit in LP, as previously observed in sporadic cases,[5] which validates the concept of the porokeratosis pathogenesis.

Patient 1 was an 83-year-old Japanese man with type 2 diabetes mellitus who presented to our hospital with annular skin lesions distributed throughout the entire body (Figure 1a). These lesions were itchy and had been present for approximately 50 years, over which time they increased in number.