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SARS-COV-2 infection: Across the border into the family

Dear Editor,

Italy has been one of the countries most affected by the COVID-19 pandemic since 21 February 2020 and, as of 18 April 2020, the Lombardy region alone has recorded 64,135 confirmed cases and 11,851 deaths, respectively 36.5% and 51% of the national burden. During the first weeks of the epidemic, before lockdown measures had been put in place, the dramatic increase in the number of patients requiring hospitalisation and intensive care led to the complete saturation of the region's hospital beds despite the rapid effort of the regional health authority to satisfy the demand [1]. At the same time, the number of laboratories equipped to confirm COVID-9 diagnoses by means of the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing of nasopharyngeal swabs was very limited. In this dramatic context, the patients who turned to the regional emergency service for influenza-like illness (ILI) were advised to stay at home and request assistance only in the case of dyspnea. However, as there was no surveillance programme with the possible involvement of general practitioners (GPs) that would have made it possible to reach mildly symptomatic subjects with suspected COVID-19, what we learned about the early spread of the disease was mainly based on hospitalised cases, and little was known about what was happening outside hospital walls.

We describe a probable cluster of SARS-CoV-2 infection involving a family nucleus living in the metropolitan area of Milan that prompts a number of considerations concerning what may have had (and still may have) a negative impact on our efforts to control the COVID-19 epidemic.

The index case was a 47-year-old Italian male civil engineer who lived with his family in the northern suburbs of Milan but worked in the Ticino canton of Switzerland. Although the lockdown in Italy was imposed on 9 March, he had a permit that allowed him to cross the border to go to work every day and, after coming into contact with a colleague who complained of a dry cough, he developed a mild fever (37.5 °C) and severe headache on 15 March. His GP advised him to take acetaminophen and stay at home in isolation from the rest of his household. On 17 March, he developed a cough that was followed by nausea and dysgeusia on 18 March, by which time the fever had spontaneously disappeared. On the same day, his 44-year-old wife and 18-year-old daughter complained of intense headache, anosmia and dysgeusia in the absence of fever and, on the following day, his 14-year-old son complained of a mild loss of smell and taste. Moreover, on 23 March, his 5-year-old daughter developed anorexia, fatigue and profound somnolence lasting for three days. On 25 March, he received a phone call from his Swiss colleague, who told him he had been diagnosed as having COVID-19. On 30 March, he informed his GP of the symptoms his wife and children had experienced, and his GP notified the health authorities that the whole family possibly had COVID-19. However, in accordance with the public health regulations at the time, none of them was tested to confirm the diagnosis and they were not put under surveillance.

On 16 April, the index case consulted an infectious disease specialist (SA), who decided to test the whole family for COVID-19 antibodies using two commercially available assays he had for research purposes: the COVID-19 IgG/IgM Rapid Test Cassette, Zhejiang Orient Gene Biotech Co. Ltd, Zhejiang, China, and the COVID-19 IgG/IgM Rapid Test, PRIMA LAB SA, Balerna, Switzerland. These tests are both based on the immunochromatographic detection of SARS-CoV-2 specific IgG and IgM in human whole blood (venous and fingerstick) serum or plasma. Briefly, one drop of capillary blood is added to the port of the test cassette, followed by two drops (approximately 80 μl) of the buffer provided with the kit, and the results are optically read after 10 min: if a coloured band is simultaneously observed at the IgM and/or IgG line and the control (C) line, the test is considered positive regardless of the intensity of the colour.

As shown in Fig. 1, the wife and children proved to be IgG positive (three by both tests, and one by the Orient Gene test alone), and the index case was also positive for IgM at the Orient Gene test.

This family cluster of probable COVID-19 cases merits a number of comments regarding the dynamics of the spread of COVID-19 and the importance of adding new controls, particularly in the light of the future gradual relaxation of containment measures. Firstly, although formally unproven, it is likely that our index case became infected outside Italy, a fact that underlines the importance of the rapid sharing of surveillance measures in order to increase our ability to detect imported cases in this globalised world.

Secondly, although the index case voluntarily isolated himself from the rest of his family as soon as he developed symptoms, it is also likely that he transmitted the infection to the rest of his family during the pre-symptomatic phase of infection. Initial studies carried out in China found that asymptomatic patients are associated with a 5% transmission rate [2], but this figure was found to be as high as 42% in a recent northern Italian study, which supports the view that asymptomatic (or pre-symptomatic) subjects have played a major role in fuelling the COVID-19 outbreak in Italy [3].

It should be highlighted that self-quarantine is not the same of isolation, a measure which separates subjects identified as infected from others who are not. Nevertheless, proactive case finding with case management as adopted by the model of Veneto Region in Italy [4] or by drive-through Coronavirus testing centers such as those employed in China, South Korea and Israel have shown to be valid measures to contain the epidemic [5].

However, although COVID-19 transmission by asymptomatic subjects is a critical factor for ensuring an effective public health response to the epidemic, the best method of identifying asymptomatic infections is still unclear. The decision not to search for SARS-COV-2 in people with mild symptoms and not to include them in surveillance programmes is at

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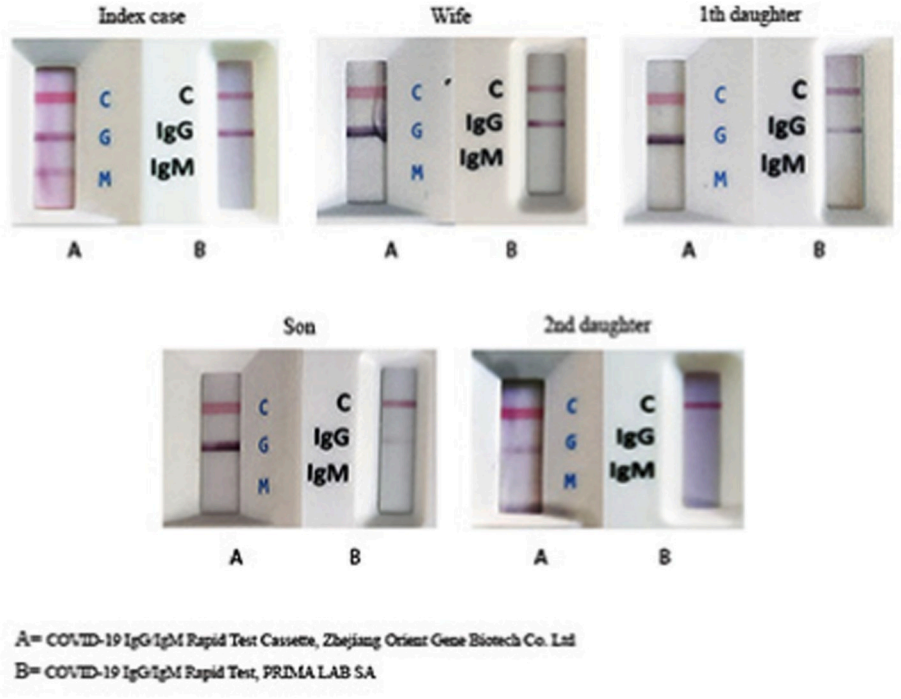

Fig. 1. Serological testing of the five family members involved in a probable COVID-19 cluster.

least questionable, particularly because the future relaxation of containment measures will require even more active surveillance in order to ensure the early detection of new cases or clusters. The clinical definition of COVID-19 has so far mainly concentrated on patients with severe disease, and much less is known about the fraction of mildly symptomatic infections not requiring hospitalisation. It is interesting to note that all but one of the family members described in this report complained of altered smell and taste, and that an increasing number of reports suggest that these are so frequent in the early phase of COVID-19 that they may be considered clinical markers of the disease [6].

Thirdly, we retrospectively identified this family cluster using two rapid serological tests. A number of such tests have become available but none have been approved by the regulatory authorities and their diagnostic accuracy is still being debated. However, the findings of recent studies suggest that they are sufficiently accurate to be used for public health purposes as well as being an invaluable epidemiological means of screening a large number of subjects.

Finally, it should be mentioned that people with suspected COVID-9 (such as the members of our family) do not appear in the official statistics concerning the COVID-19 epidemic. Given that it is unlikely that ours are an isolated event, it is possible that overlooking mildly symptomatic cases is leading to a serious underestimate of the real burden of COVID-19.

Credits

SA: conceptualisation, writing & editing; AT: writing & editing; CA: conceptualisation, diagnostic testing, writing; CB: writing & editing; SS: writing & editing; ALR: conceptualisation, writing & editing; MG: writing & editing.

Consent for publication

Written informed consent was obtained from all of the subjects, including the parents of the children.

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Declaration of competing interest

None of the authors has any conflict of interest to declare.

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