

**LETTER**

**How to manage children if a second wave of COVID-19 occurs**

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Dear Editor,

Many experts believe that those countries that presently have an acceptable rate of COVID-19 transmission may experience a second wave of COVID-19 as we enter the colder months of autumn

and winter.<sup>1</sup> The results from studies performed during the first wave of the pandemic could be useful in preparing for a second wave, reducing its impact on health systems, while also imposing fewer restrictions to contain the spread. Children are more frequently asymptomatic or undergo a milder form of disease than adults.<sup>2</sup> Contrary to what happened in the first weeks of the pandemic, when children with signs and symptoms compatible with COVID-19 were hospitalised irrespective of the diagnosis and disease severity, if a second wave occurs most children with suspected COVID-19 could be cared for in the community. This would significantly reduce hospital overload and related problems. Telemedicine and the availability of well-functioning community health houses (CHHs) could be effective in this regard (Figure). A recent Italian experience has shown that the use of a telemedicine service specifically devoted to parental support and primary care paediatricians of children with suspected SARS-CoV-2 infection offers timely and rapid care, reducing the need for hospital admission.<sup>3</sup> Intermediate structures between primary care paediatric surgery and the hospital, such as CHHs, could be even more effective in confirming suspicion of COVID-19. By performing basic laboratory investigations, including diagnostic swabs at the patient's home or in an outpatient setting, selecting subjects in need of hospitalisation, and organising home monitoring for those with mild COVID-19, would reduce the burden on hospital settings. In the Emilia-Romagna Region, we demonstrated that less than 1% of the SARS-CoV-2-positive children followed at CHHs were subsequently hospitalised, whereas all of the positive cases presenting to Emergency Units were hospitalised.<sup>3</sup>

In the event of a second wave, a second issue that should be approached differently concerns the role of children in infection transmission. At the beginning of the pandemic, and based on the experience with influenza,<sup>4</sup> children were considered among the main groups likely to be responsible for SARS-CoV-2 transmission. To reduce risk, any type of school was closed including day care and children's social care centres. However, evidence has emerged that the incidence and severity of COVID-19 is significantly lower in children than in adults, which has raised substantial doubts about the logic of this decision and its practical value.<sup>5</sup> Support for fewer restrictions to children's lives was provided by recent studies that have shown that in most cases children are infected by adults, whereas the risk of infection from child to child or from child to adult is marginal.<sup>6</sup> Moreover, countries that reopened schools during the pandemic notably had no increase in COVID-19 incidence.<sup>7</sup> Finally, mathematical models based on available epidemiological data have indicated that school closures have only a limited effect on COVID-19 incidence and no impact on mortality.<sup>8</sup>

Further support for avoiding restrictions on children's lives could be derived from a number of biological studies that are seeking to explain why SARS-CoV-2 infection is different in the paediatric population. In nasal epithelial samples, the expression of angiotensin-converting enzyme

2 (ACE2), the receptor used by SARS-CoV-2 for entry into host cells, is strictly age-related and was found to be significantly lower in younger children than in older subjects.<sup>9</sup> This finding seems to indicate that a delay in tissue maturation can be helpful in decreasing the acquisition of SARS-CoV-2 infection and disease development. Moreover, a role could be played by lymphocytes, i.e., blood cells with an essential role in host defences. In contrast to adults with COVID-19, who if severely affected, have relevant lymphocytopenia, children with COVID-19 generally have a normal lymphocyte count,<sup>10</sup> suggesting less immune dysfunction. On the other hand, healthy younger children have a greater number of lymphocytes than adults, and it has been postulated that this feature could be the consequence of continuous immune system activation due to frequent infections. Also, trained immunity memory can be important. Repeated stimuli by frequent infections can result in an enhanced innate function that may protect older children.<sup>11</sup>

Although it seems likely that most children do not have a role in the diffusion of SARS-CoV-2 infection, it remains to be explained why a minority of children develop a serious, sometimes life-threatening disease. How can children at risk be identified and treated early and what is the role of these subjects in the diffusion of infection? The best example in this regard is multisystem inflammatory syndrome (MIS), which in some cases resembles Kawasaki disease, and is characterised by clinical and laboratory signs of cytokine storm syndrome.<sup>12</sup> In some studies, the predominance of this condition in children of Hispanic/Latino and Black/African American ancestry was reported, and genetic susceptibility has been considered.<sup>13</sup> On the other hand, as in Kawasaki disease, in MIS cases increased serum interleukin (IL) 6 concentrations are common. In children with Kawasaki disease, variants in Toll-like receptor 6 (TLR-6) have been identified, and it has been shown that subjects homozygous for the intronic risk allele (A allele of TLR6 rs56245262) had differential expression of IL-6 as a function of genotype ( $P = 0.0007$ ).<sup>13</sup> Further studies are needed to identify children at risk of SARS-CoV-2-related complications who require anti-IL-6 therapy.

In conclusion, while waiting for the publication of further studies on paediatric COVID-19, we recommend that school closure, which can have a negative social, psychological and economic impact, particularly among the youngest students, should be avoided.<sup>5,14</sup> Notably, the infrastructure of schools should be adapted, staff to pupil ratios addressed and appropriate education on infectious disease prevention provided to assure safe conditions.<sup>15</sup> Furthermore, guidelines at the local level on how to manage classes in the presence of an infected student, or teacher are needed. In addition, the impact of schools remaining open in different settings (e.g., Africa and Latin America) and during periods when SARS-CoV-2 circulation is high, should be further evaluated.

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**Figure.** Telemedicine information flows between families, hospitals, paediatric centres and health facilities

