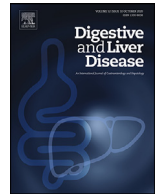




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## Editorial

## Children and Fecal SARS-CoV-2 shedding: Just the tip of the Iceberg of Italian COVID-19 outbreak?



### 1. Introduction

As of June 18, 2020, 8061,550 cases of infection by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) known to cause Coronavirus disease 2019 (COVID-19) were reported worldwide with 440,290 deaths [1]. Italy was one of the first affected countries, experiencing a particularly high incidence and case fatality rate (CFR). Totally, 237,695 documented infections have been reported in Italy, with the Northern Regions accounting for almost two-thirds of cases [2]. Age distribution shows that only 2.2% of cases affected children (<18 years old); thus, pediatric patients (<18 years old) appeared to be at low-risk and not a major concern (only 4 deaths reported) [2]. To date, it is still unclear how this pandemic has spread in Italy, particularly in the Northern Regions, and why in those zones the incidence is currently higher than in the rest of the Country, despite the considerable cases reduction nationwide. Information regarding the disease spread in children is of relevant importance for transmission control and appropriate healthcare policies. Recently, interesting data surfaced questioning the role of children as infection carriers due to the prolonged fecal viral shedding. This point represents an intriguing aspect to understand the beginning of the Italian epidemic.

### 2. Infection in children is likely under-reported

All available data confirmed that children have less severe disease with fewer or nonspecific symptoms, difficult to distinguish from common pediatric infections [3,4]. Italy's pediatric infection rate could be underestimated as the majority of clinical testing facilities were reserved for severe cases due to the fact that the public health system was overwhelmed. On February 25, a stop testing policy was implemented for asymptomatic contacts after the spread of the infection in the Northern Regions. By comparison, China, USA and South Korea showed higher rates of pediatric infections (4–6%) [4,5]. In the initial Chinese pediatric report, more than 50% of children were either asymptomatic or presented mild disease [6]. While many children presented symptoms of acute upper respiratory tract infection, others had no fever or only exhibited gastrointestinal (GI) symptoms, including nausea, vomiting, abdominal pain and diarrhea. Children were tested in the high-risk province of Hubei, however, not for clinical suspicion of infection [6]. This would suggest that many children in Italy might have been affected without being officially reported, especially in the north.

The rate of SARS-CoV-2 infected children in South Korea was reported to be the highest (6.2%), likely due to prominent testing combined with extensive efforts to isolate, track and quarantine infected people and their contacts [5]. This raises the question whether the actual rate of infected children worldwide could be larger considering the paucity of tests performed in the pediatric population.

Moreover, the chance of finding infected children increases if all cohabiting family members are tested after an index case [7]. This observation confirms that SARS-CoV-2 transmission is most likely among individuals sharing a household. Children are mostly asymptomatic or pauci-symptomatic and this should be considered in analyses of transmission and control. Asymptomatic household transmission can cause severe COVID-19 pneumonia with a communicable period up to three weeks long [7]. However, the epidemic peak in Chinese children occurred two weeks later than that in adults, suggesting a longer incubation period [8]. This finding indicates that the quarantine period for children who had contact with confirmed patients should be longer.

Finally, the national lockdown measures may have promoted an unknown higher number of people, children included, that have been managed by home care without official detection. During the lockdown, the vast majority of children were evaluated by telemedicine or phone calls due to the enhanced safety measures and to the fact that the hospital facilities were overwhelmed.

### 3. Gastrointestinal involvement and elimination of the virus in stools

GI involvement is another possible reason for considering the actual rate of pediatric cases higher than that officially reported, as several children only present digestive features [3]. Studies have identified SARS-CoV-2 RNA in anal/rectal swabs and stool specimens of COVID-19 patients even after upper respiratory tract virus clearance [9]. The viral receptor angiotensin converting enzyme 2 (ACE2) was found to be expressed in the epithelial cells of upper, lower and small intestine [10]. SARS-CoV-2 can actively infect and replicate in the GI tract and diarrhea can be one of the initial symptoms in up to 50% of cases [11]. In contrast to what observed in adult patients, higher proportions of fever, vomiting, and diarrhea were recorded on admission in pediatric cases [12]. Unfortunately, clinical management of children with GI symptoms did not include COVID-19 evaluation before the knowledge of pandemic.

GI localization in children may represent an alternative site of viral shedding and transmission. Since SARS-CoV-1 can be transmitted through fecal-oral dissemination [13], SARS-CoV-2 could follow the same path [14]. SARS-CoV-2 is 79.5% identical to SARS-CoV-1, sharing the same receptor. This is particularly relevant considering an environmental study suggesting that SARS-CoV-2 could remain on plastic and stainless steel for up to 72 h. A recent meta-analysis confirmed that a significant proportion of infected patients had positive SARS-CoV-2 RNA detected in their fecal specimens [15]. Although, the method of detection does not differentiate between live and dead viruses, fecal contamination of objects in the environment as a means of transmission should not be neglected.

The extra respiratory transmission of the virus is compatible with the rapid spread of COVID-19, especially in Italian Northern regions in which the higher diffusion is yet to be explained. Physicians and caregivers of potentially infected children need to be aware that stools might be infectious. The existing literature, however, remains inadequate to fully understand the GI involvement of SARS-CoV-2, in terms of pathology, prognosis and treatment.

#### 4. School closure dilemma

There is a lot of debate worldwide regarding school closure. Most Countries opted to close schools considering historical findings on 1918–20 influenza pandemic mitigation measures without clear evidence on COVID-19. Closures support social distancing, aid in lowering the epidemic curve and encourage family members to stay home. On the other hand, the school closure might have detrimental psychological effects and unpredictable consequences on children's health [16]. However, restrictive policies controlled COVID-19 more in children than in adults, with fewer cases confirmed during the lockdown, which may be due to the low susceptibility, as well as the reduced contacts.

Looking at the outbreak in Italy's Northern Regions during the early phase of the epidemic, there was a significant temporal discrepancy between school closures in Lombardy (February 25) and the complete lockdown on major business activities (March 7). This delay could have forced many undiagnosed or infected children to stay at home while parents continued working and interacting with others. This in turn may have led the elderly, who could be looking after the children, to be exposed to possible infection carriers by fecal-oral transmission.

Moreover, there is evidence that the virus arrived in Lombardy long before the first case was officially identified in Codogno [17]. A recent study shows that pediatric patients with COVID-19 became infected not only by close contact with infected adults, but even by exposure to epidemic areas [18].

Based on this finding, we cannot exclude that many children could have been infected before school closures. In this case, school children could have transmitted the virus to members of household, where basic hygiene procedures and person-to-person transmission of germs occur in close proximity. The long fecal viral shedding might be the link in the transmission chain between school, community and home. The risk of family cluster transmission from children harboring the virus and its impact on community-based epidemic prevention should be taken into consideration in policy making for epidemic control.

To support this hypothesis, we have considered the most affected Northern cities in the early phases of the epidemic (Codogno) that have efficiently contained the outbreak after a simultaneous total lockdown. In neighboring Bergamo and Brescia, the total lockdown was enforced 11 days after school closures and the delay most likely contributed to the spread of the infection despite initial mitigation measures. This could partially explain the delay in obtaining sound results after lockdown. In the South of Italy, the numbers of cases were low at the time of the national

lockdown and have remained lower than those in the Northern regions.

However, before drawing definitive conclusions, more detailed data are required on the role of infected children in COVID-19 epidemiology.

Since the outbreak seems to be in a more controlled phase in Italy, the decision of re-opening schools should consider the time period of SARS-CoV-2 fecal shedding and transmission risks among children. Re-opening may trigger a second wave in the community. Standardized measures should be prepared (i.e. detailed school guidelines, disinfection, diagnostic tests, and contact management) in the event of new positive cases. To achieve stringent case detection in the school community, a type of specimen that can be self-collected at home would be necessary. Testing stool samples could be an option for community wide screening, especially for children for whom it is difficult to collect a reliable respiratory sample by parents.

Despite everything, more attention should be paid to pediatric cases and fecal viral shedding. If children are important in viral transmission and amplification, social and public health policies (e.g., avoiding interaction with elderly people) could be established to slow down transmission and protect vulnerable populations.

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