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COVID-19 in Children: Looking Forward, Not Back

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Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children; RT-PCR, reverse transcription polymerase chain reaction; SAR, secondary attack rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

In the fall of 2020, some of the fiercest debates waged in both academic and public arenas concern the relative ability of children to acquire and transmit SARS-CoV-2, the causative agent of COVID-19—rightfully so, as there are enormous implications for children, parents, and schools. To date, much of the data have come from studies of COVID-19 within household clusters early during the pandemic. In this issue of *Pediatrics*, Laws and colleagues add to this body of literature with a secondary analysis of a previously reported household contact study.[1] They describe infection rates, transmission dynamics, and symptom profiles in a cohort of US children with household SARS-CoV-2 exposure between March and May 2020 in Milwaukee and Salt Lake City.[2]

The authors found that secondary infection rates in household contacts was similar in children (19/68 contacts; 28%) and adults (36/120 contacts; 30%). Having an infected parent was associated with a marked increase in risk for secondary infection in a child. Possible child-to-adult or child-to-child transmission was observed in 2/10 and 1/6 households, respectively, with potential for such events. Infected children generally had mild symptoms and were less likely than adults to report lower respiratory tract symptoms or loss of taste or smell. The findings provide additional confirmation that the overwhelming majority of children with SARS-CoV-2 infection develop mild symptoms,[3,4] but question whether children are less susceptible to infection or less likely to transmit SARS-CoV-2. Limitations of the study include convenience sampling and relatively small sample size, as only 33 households analyzed included children.

Household contact tracing studies similar to that conducted by Laws and colleagues arguably provide the best evidence regarding pediatric susceptibility to SARS-CoV-2, where the intensity of exposure between household contacts is higher and more consistent than in non-household settings. While not universal,[5] the preponderance of data from numerous countries

continues to support the notion that children are less susceptible to infection than adults.[6-13] Recent meta-analyses suggests that overall susceptibility in children is approximately half of that of adults, with the greatest effect seen in younger children.[14,15] In this study, younger children had lower rates of infection: the odds ratio for infection in 5-12 year olds compared with 13-18 year olds was 0.36 (95% CI, 0.13-1.05).[2] Notably, virtually all previous studies have relied on RT-PCR to detect infection and often only test symptomatic contacts. That four pediatric infections in this study could only be detected by antibody seroconversion suggests that RT-PCR-based case detection (symptoms-based or otherwise) in children may underestimate true infection prevalence.

At the population level as well, children continue to be underrepresented among SARS-CoV-2 infections. Numerous large-scale studies have indicated that children, particularly children <10 years, have much lower rates of infection than do adults.[16-19] In the US however, between August 27 and September 10 pediatric SARS-CoV-2 infections increased from 9.5% to 10% of all infections, reflecting a months-long summer trend where regions experienced severe outbreaks and physical distancing recommendations were relaxed or ignored as testing capacity increased.[20] While concerning, children under 18 represent 22.3% of the US population,[21] and this increase has been driven primarily by infections in older children.

The role of children in transmission of SARS-CoV-2 is similarly problematic. This study found that 20% and 17% of households had potential child-to-adult transmission and child-to-child transmission, respectively, but numbers are too small to draw definitive conclusions. Despite some reports of likely onward household transmission from infected children,[22,23] most studies suggest that children appear less likely to transmit compared with adults or present as index cases in household clusters.[7,13,19,24-26] A study from South Korea generated considerable

alarm when it reported that children 10-19 years old appeared as likely as adults to transmit infection to household contacts.[27] However, a subsequent, more detailed, analysis of 107 pediatric index cases and their household contacts found definitive evidence of only one instance of onward transmission from a teenager, giving a household SAR of 0.5%.[28]

A significant limitation of household cluster data is that most were generated during school closures, when opportunities for non-household exposure to SARS-CoV-2 among children were scarce. Newer data--reporting experiences in summer camps, childcare settings, and schools (both pre-closure and post-reopening) are helping to fill this gap. Importantly, in areas with low prevalence rates and appropriate mitigation policies, children occasionally become infected but there have been no significant outbreaks. For example, schools or child care programs systems in Ireland, Australia, France, Singapore, Germany, and Rhode Island reported no to little facility-based transmission of SARS-CoV-2 by children despite the presence of infected children.[29-34] However, in areas with widespread community transmission or less strict mitigation procedures, large outbreaks have occurred.[35-38] Consistently, these outbreaks reveal that infected adults are typically responsible for introducing virus into these settings, questionable testing strategies enable outbreak initiation, and inconsistent use of masks or cloth facial coverings makes containment of the virus challenging.

So where does this leave us now? First, children clearly are capable of acquiring and transmitting SARS-CoV-2. Second, the preponderance of current data still indicates that children have reduced susceptibility and infectivity compared to adults, though this requires further monitoring as increased testing capacity and relaxation of community mitigation may continue to diminish the magnitude of these differences, which were so stark early during lockdown periods.

Third, the importance of mitigation measures, especially the use of masks, including among children, is now incontrovertible.[39]

Moving forward, there remains a critical need for more high-quality pediatric SARS-CoV-2 research. Studies in children are often limited by small sample sizes and binning into convenient age cohorts that belie important differences in biology and behavior. The starkest example is to group all children <18 as a single age cohort, when there is ample evidence that younger children and older teens represent completely different patient populations in the context of SARS-CoV-2. For example, in the same region of France, higher rates of potential school-based transmissions were apparent in high schools compared to primary schools.[38,40] A major step forward in pediatric SARS-CoV-2 research would be universal establishment of reasonable age strata to enable more appropriately powered and comparable studies. Elucidating the mechanisms responsible for differences in symptomatology, susceptibility, and infectivity between adults and children will remain important. However, at this point we also need to shift our focus towards the interventions most important for minimizing transmission of SARS-CoV-2 to and from children, understanding the pathogenesis of MIS-C, and advocating for appropriate pediatric clinical trials for SARS-CoV-2 vaccine candidates.

As SARS-CoV-2 continues its inexorable march through susceptible populations, we must remember that there is no setting on Earth guaranteed to be safe from SARS-CoV-2. With that sobering recognition, we must work to fulfill the medical, academic, social, and emotional needs of children, despite knowing that providing such care cannot ever be completely free of infectious disease risk. As has been shown in the US and around the world, with appropriate mitigation strategies, we can successfully minimize (although not eliminate) the risk of COVID-19. We fear that one day, we will look back on this terrible pandemic and recognize the extent to

which we have failed our children, by being more afraid of their infection and transmission risks than of the prospect of letting them down precisely when they needed us most.

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