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Kids & COVID: Part Two
New Insights into Potential Problems Warrant Caution

Rob Graham, R.R.T./N.R.C.P.

I dedicate this column to the late Dr. Andrew (Andy) Shennan, the founder of the perinatal program at Women's College Hospital (now at Sunnybrook Health Sciences Centre). To my teacher, my mentor and the man I owe my career as it is to, thank you. You have earned your place where there are no hospitals and no NICUs, where all the babies do is laugh and giggle and sleep.

" It pains me to report that this virus is far from over with us; it is no lady, has no etiquette, and knows not the appropriate time to take its leave. So, here we go again."

To say that we're all "done" with this pandemic, I suspect, will garner unanimous agreement. Whether one is a healthcare worker dealing with this everchanging pathogen, a parent at wits end trying to work from home while dealing with homeschooling, or even an "anti-vaxxer," "Covidiot," or conspiracy theorist, it is a universally shared sentiment. It pains me to report that this virus is far from over with us; it is no lady, has no etiquette, and knows not the appropriate time to take its leave. So, here we go again.

Research into the ongoing pandemic is proceeding at a furious pace such that freshly published information may be obsolete or incomplete shortly after dissemination. Immediately after December's COVID & Kids column, new studies, some preprint, offer insights into how COVID-19 produces its path of destruction and show increasing evidence of an emerging potential public health catastrophe and how it happens: Long-Covid.

We are also discovering more about the Omicron variant (OV) and a new variant of concern in France identified as "IHU." Initial (unconfirmed) reports speculated IHU (suspected to have originated in Cameroon) was even more contagious than OV, which is currently the dominant strain in France. The type and location of IHU mutations support the premises of both its contagiousness and vaccine/immune evasion. The fact that the first identified French patient had been vaccinated also supports the latter. The small number (12) of IHU cases identified and the fact that OV is by far the dominant strain in France may indicate decreased transmissibility of IHU. Still, too many factors are at play, and it is too early to draw any conclusions (1) (preprint).

In December, I reported on rising cases of children in hospitals in several U.S. states, namely New York and Arkansas. These reports continued to come out of other areas like LA County. Since then, the OV has exploded worldwide, and we are seeing paediatric hospitalizations rising in Canada.

Initial data from South Africa indicated OV was not as likely to result in severe disease but that the variant seemed to be attacking more young children, and symptomatically at that. Understandably the world grabbed onto news of "milder" infection and held on for dear life. Recent data out of Ontario, Canada appears to reflect the South African experience showing a 65% decrease chance of hospitalization with OV c.f. Delta variant (DV) and risk of hospitalization & death 83% lower with OV (2). (This data was gathered between November 22 and December 25, 2021, so it does not represent the current post-holiday exponential surge in OV in Ontario).

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What is being found is hospitalization for children is increasing in Ontario, and children's hospitals are preparing for a surge. While only nine deaths have been reported in those <19 to January 7, 2022, this vastly underrepresents OV. That number includes two children under age six dying in the past week, variant unreported (3). As of January 6, 2022, 51 children <5, 9 children 5-11, and 8 children 12-19 were hospitalized in Ontario. Those <5 are currently ineligible for vaccination, which may partially account for their disproportionate numbers in the hospital (there were 4830 <5 infected at the time of reporting). Ontarians >12 have been vaccine eligible since May 23, 2021 (currently 16530 cases, 82.1% fully vaccinated) and those 5-11 (currently 11112 cases, 1.7% fully vaccinated) since November 23, 2021 (4,5). Since children do not require hospitalization nearly as much as adults do, there

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is a paucity of paediatric hospital beds, especially intensive care beds, relative to available adult facilities. A smaller fraction of children getting seriously ill could easily overwhelm our ability to treat them.

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With OV, a disturbing trend is emerging: breakthrough infection. In Ontario, 88% of those >12 are fully vaccinated (x2), and 3rd "booster" doses are being rapidly deployed; 72.4% >80 and 69.1% 70-79 are "boosted" with all >18 eligible. Despite Ontario's level of vaccine uptake, current hospitalizations paint a stark picture; 572 non-immune (no or partial vaccination) patients are in hospital (non-ICU) compared to 1353 fully vaccinated patients. One hundred forty-one non-immune patients are in ICU, while 137 fully vaccinated occupy ICU beds, a statistical tie. As of January 8, 2022, Ontario has 13745 active cases. Of these, a staggering 10865 are fully vaccinated. This demonstrates the ability of OV to evade vaccine-induced immunity while simultaneously showing the protective effect of vaccination; 12.45% vaccinated in non-ICU beds and 0.126% in ICU. Comparing the nearly 20% of the non-immune cases in the hospital and nearly 5% in ICU makes a compelling argument for vaccination regardless of OV's immune avoidance capability (6).

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Preliminary analysis of OV infections in Ontario supports the reassuring premise that OV universally does not result in as severe an illness as Delta variant (DV) (7). What is not comforting is rapidly accumulating evidence that recovery from even mild infection may be followed by "Long Covid" (LC): 203 symptoms that may persist at six months or more post-recovery, and that 1 in 7 Covid-19 (C19) infected patients remain symptomatic at 12 weeks (8). One comprehensive analysis found at least one symptom present after six months in 54% of cases, regardless of hospitalization status (9).

OV replication occurs primarily in the nasal and oropharyngeal tract but not in deeper pulmonary tissue, but it appears to infect more cell types than other variants readily. This and its rapid replication in the nasal cavity (up to 100 times faster than DV) contribute to its high transmissibility early in its course. Still, titers decline rapidly after 24 hours (10) (preprint). While OV is less contagious than measles (currently the most contagious virus we know of), its short incubation period makes it effectively more contagious. With a doubling time of 1.5 – 3 days c.f. measles 15 days, a single case of measles becomes 50600 cases at 60 days, while OV results in a staggering 244,000,000 (11).

What are the long-term implications? While one is less likely to end up in hospital with OV, C19 pneumonia is far less prevalent with OV. Unfortunately, OV's ability to infect other organs, including the brain and nervous system, is quite intact, perhaps even more so (10). Follow-up studies have found the presence of C19 virtually everywhere (12) (preprint) and raised concerns about neurological sequelae (13). A post-mortem study found changes in the brain. Still, it could not identify these as being directly caused by C19 (14), while a British study comparing pre and post C19 brain imaging found a host of alterations compared to controls (15). While the long-term significance of these alterations remains to be seen, any alteration in brain structure is concerning. This is particularly true if these alterations occur during neurodevelopment, and LC in children is a real concern.

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This brings us back to C19 and kids. With more children infected with OV, we will indubitably see more neurological symptoms. One post-mortem case report on a 14-month-old infant showed extensive damage to multiple systems (16). The Kölliker-Fuse nucleus (KFN) is a structure within the brainstem intricately linked to upper airway control, swallowing, and vocalization. While normally fully developed at birth, neurochemical alterations/dysfunction in the KFN have been implicated in sudden infant death syndrome and Rett syndrome (17). Two case reports are particularly troubling in young children, a 16-month-old girl and a 17-month-old boy (previous 34 week PCA with uneventful NICU stay) infected with C19. These children presented with new-onset solid food aversion, and the girl lost her limited vocabulary suggesting KFN dysfunction (18). (I would like to thank Dr. Denise Dewald for bringing the aforementioned case reports to my attention).

It has been recently discovered that C19 produces an autoantibody response, particularly in women post asymptomatic infection and in men with mild symptoms at a minimum (19). This may help explain a significant increase in newly diagnosed diabetes >30 days post C19 infection in those <18 thought to be caused by the infection (20). (The quality of this CDC study is facing a great deal

of criticism from academia). Whether or not this has implications for a host of other autoimmune disorders remains to be seen, and it may be years before we can answer this question.

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"It may be too early to determine if OV causes less severe disease. While hospitalization during acute illness may be decreased in adults, it is increased in children. Time will tell, but we do not have enough evidence yet to label OV as less worrisome. Given the plethora of systems affected by C19 infection, the possibility remains that OV is not less severe; it may just take longer to kill."

Several studies have found an increased risk of death following C19 recovery (60% higher than the general population), especially in those who've had a severe illness or are elderly. Eight excess deaths per 1000 patients occurred in all C19 survivors, but if hospitalized, that number increases to 29 (22). Symptomatic infection in children prior to OV has been rare, hospitalization even more so. A surge in children in hospital with OV begs the question of mortality risk post-recovery in children, and the incidence of newly diagnosed autoimmune or other diseases in recovered children should be closely followed. LC has not seemed to spare children with previous C19 variants. While "milder disease" (at least initially) seems to be the hallmark of OV, the increasing number of children ill enough to require inpatient care suggests this is not the case for this cohort. It is too early in the OV wave to draw reliable conclusions, but it is reasonable to assume OV will result in as much LC in children as we've seen to date, if not more so.

It may be too early to determine if OV causes less severe disease. While hospitalization during acute illness may be decreased in adults, it is increased in children. Time will tell, but we do not have enough evidence yet to label OV as less worrisome. Given the plethora of systems affected by C19 infection, the possibility remains that OV is not less severe; it may just take longer to kill. In any event, the sheer number of people almost certain to be infected with OV may make its relative severity a moot point from a systemic perspective; it's folly to expect a smoother ride from this point on.

Finally, there is a hidden pandemic within the C19 pandemic. It is estimated that worldwide, 1,134,000 children had experienced the loss of at least one primary caregiver, and 1,562,000 had lost at least one primary or secondary caregiver as of April 30, 2021 (23). This has major socioeconomic and developmental implications for children, families, and society.

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Those working in healthcare have endured a living hell for the past two years. While those of us in the NICU have largely been spared the agony of watching our charges succumb to this horrible virus (their parents not so much), we have not been spared the constant stress of wondering and worrying if one of our loved ones or we will be C19's next victim. It is vitally important for us to take time out to de-stress. Smell the flowers. Pet the dog (or cat if it's in the mood!). Enjoy your favourite foods, watch your favourite shows, go for a walk. Avail yourself of whatever support services available to you; seeking help is a sign of strength, not weakness. Life goes on, C19 notwithstanding; it has taken far too much from us already. If we surrender our happiness, its victory will be complete.

Be well. Stay safe. And a happy new year!

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Disclosures: The author receives compensation from Bunnell Inc for teaching and training users of the LifePulse HFJV in Canada. He is not involved in sales or marketing of the device nor does he receive more than per diem compensation. Also, while the author practices within Sunnybrook H.S.C. this paper should not be construed as Sunnybrook policy per se. This article contains elements considered "off label" as well as maneuvers, which may sometimes be very effective but come with inherent risks. As with any therapy, the risk-benefit ratio must be carefully considered before they are initiated.

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