COVID-19 disease spectrum in children – first insights from Africa

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Although the morbidity and mortility observed among older people with SARS CoV-2 infection is high, a consistent observation has been the low risk of severe disease in children and young adults (1,2). In fact paediatric intensive care units were often converted to accommodate adult patients in countries with major epidemic peaks that overwhelmed the healh care system, given the low numbers of children requiring intensive care compared to older adults. The pronounced age differential observed with severe COVID-19 disease is different to the experience with SARS or major influenza epidemics of the past and remains largely unexplained (1).

Despite their relative protection against adverse outcomes, instances of severe disease in children do occur (3,4) and it is important to better understand the risk profile of these children. In addition, disease rates in low and middle income countries (LMICs) with higher rates of childhood malnutrition and human immunodeficiency virus (HIV) infection have not been reported. Given that children in LMICs experience increased vulnerability to other severe lower respiratory tract infections (5), this is an important knowledge gap. To date, there has been no comprehensive overview of the COVID-19 disease spectrum observed in children from sub-Sharan Africa where malnutrition and HIV infection rates are high.

In this edition van der Zalm et.al. report on all children (<13 years of age) with laboratory confirmed SARS CoV-2 diagnosed at Tygerberg Hospital in Cape Town, South Africa (6). The study was conducted during the time that Cape Town represented the epicentre of the SARS CoV-2 epidemic in South Africa. In total 159 children were identified with infection, of whom 51 (32%) were hospitalized with COVID-19 disease. Only one child requiring hospitalization was HIV infected, which does not suggest major vulnerability resulting from HIV infection in young children; given the relatively high prevalence of HIV infection in the communities served by Tygerberg Hospital. Although malnutrition was common, it was also not associated with hospital admission or the likelihood of severe disease; defined as a peripheral O^2 saturation of <94% requiring oxygen supplementation.

Some form of respiratory support, mostly high flow nasal prongs oxygen, was required in nearly half (25/51; 49%) of the hospitalised children; of whom the majority (13/25; 52%) was younger than 3

months of age. As has been the experience in other southern hemisphere settings where strict social distancing measures were in place throughout winter, total hospital admissions for respiratory infections were greatly reduced compared to historical averages. Despite the presence of SARS CoV-2 Tygerberg Hospital experienced a greater than 30% reduction in paediatric admissions due to respiratory infections during the study period, compared to the same period last year. This reflects the major impact that social distancing has had on the transmission of common respiratory viruses, with a concurrent reduction in secondary bacterial infections.

Among children admitted to ICU there was a high rate of virus co-infection, which is common in children with respiratory disease (7). This poses a major dilemma for cause attribution and differentiating true pathogens from incidental detections. It is difficult to know what contribution infection or co-infection with SARS CoV-2 made to the severe disease experienced by these co-infected cases. It is also important to remember that disease descriptions from teriatry referal hospitals, such as Tygerberg Hospital, amplify the severe end of the disease spectrum and concentrate children with comorbidities. The authors excluded children in whom there was no clinical indication to perform the test and specified variable testing guidelines that we in place during different periods of the study, which at least provides a greater appreciation of potential selective bias.

Although steroids are indicated for severe COVID-19 disease,(8) the majority of children received steroids before SARS CoV-2 infection was confirmed, based on clinical indications in the study setting where infants with signs of non-acute respiratory infection and hypoxia are routinely treated for *Pneumocystis jiroveci* pneumonia (PJP) until this has been excluded. In the absence of a compartor group it is impossible to assess the role that early steroid administration may have played to reduce disease severity. Diarrhoea and vomiting, as well as the rare multisystem inflammatory syndrome (MIS-C), was more common in older children and acute appendicitis was recognised as a potential gastro-intestinal presentation of SARS CoV-2 infection in this group (6,9,10).

It is notable that a high percentage of children admitted to hospital (7/51; 13·7%) had a recent or new diagnosis of tuberculosis. Globally, the SARS CoV-2 pandemic has had a major detrimental impact on TB control efforts, mainly through reduced and delayed case detection and increased treatment

default caused by difficulties in health care access and treatment supervision (11). Since more than 90% of children less than 3 months of age with severe COVID-19 received BCG vaccination, the authors concluded that this suggests lack of protective effect. The protective effect of BCG against COVID-19 remains highly contentious, but study observations do not provide new insight. Given that BCG induced immune responses are only activated 2-3 months after administration, the over-representaiton of children under 3 months of age among those with severe COVID-19 may suggest a protective effect rather than than the absence of a protective effect. However, given the myriad factors that increase vulnerability to severe infections in babies under 3 months of age it is important to guard against over-interpretation.

Returning to the pronounced age differential in COVID-19 disease vulnerability referred to earlier, it is interesting to review basic principles. It may be that young people are less likely to get infected with the virus, or that the virus is less likely to reach their lungs. From the available epidemiological evidence there is no indication that young children are less likely to become infected than older people,(12) although they may excrete the virus for a shorter period of time and unlike the situation with other respiratory viruses they contribute little to community spread (13). The same cannot be said of younger adults with high levels of social contact who may contribute substantially to community transmission, although they are at low risk of disease development themselves (14).

There is general consensus that primary SARS CoV-2 infection usually occurs in the upper airways. Although aerosol transmission with direct lung infection can occur, this seems to be rare and most people develop pneumonitis after a period of upper airway symptoms. Whether the virus ends up in the lung via contiguous spread along the airway, or via occult aspiration events remains to be determined. However, occult aspiration could partially explain the pronounced age and gender related differences observed, as well as reported associations with morbid obesity in younger people and possibly even the increased risk observed in young infants (<3 months of age). Once pneumonitis is established it is clear that excessive and dysregulated immune responses underlie the acute respiratory distress syndrome (ARDS) and/or systemic inflammatory response syndrome (SIRS) associated with respiratory and multi-organ failure, which represents the most common terminal pathways following SARS CoV-2 infection.

In general the report from South Africa contains good news about COVID-19 disease risk in HIV-infected and malnourished children, and supports observations that children are generally a low risk group. However, infants (especially those <3 months) hospitalized with SARS-CoV-2 frequently required respiratory support. The unavailability of continuous positive airway (CPAP) ventilation or even humidified oxygen via nasal prongs is a major concern in many LMICs, for optimal clinical management of severe COVID-19 and common childhood pneumonia (6,15). In children with severe COVID-19 there is also a need to better characterise longer term sequellae.

Conflict of interest: I declare that I have no competing interests

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