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CHILDREN ARE STILL SAFE FROM COVID-19 WITH SCHOOLS REOPENING – AN IMMUNOLOGICAL PERSPECTIVE
Dr Samuel Matoya Nyamweya (Immunologist), Egerton university, Dept of Human Pathology, P.O. Box 536-20115, Egerton. Email: samuel.nyamweya@egerton.ac.ke

CHILDREN ARE STILL SAFE FROM COVID-19 WITH SCHOOLS REOPENING – AN IMMUNOLOGICAL PERSPECTIVE

S. M. Nyamweya

ABSTRACT

Aim: **Countries have eased restrictions and in Kenya children have even been allowed back to school. Several parents still have fears about the health of their children as they go back to school after a long break occasioned by the COVID-19 outbreak. In this review, we aim to provide the immunological basis for our argument and thus opine that it's safe to have the children in school.**

Content: **The coronavirus disease 2019 (COVID-19) pandemic caused by SARSCoV-2 has affected many people worldwide, but data on how it affects children are rare. Children have so far accounted for 1% - 5% of diagnosed COVID-19 cases. A general pattern reported from multiple countries shows that those children who test positive for COVID-19 experience a mild form of the disease and have a better prognosis than adults. Deaths are extremely rare or low. Diagnostic findings show that compared to adults, elevated inflammatory markers are less common, lymphocytopenia seems rare, and fewer children develop severe pneumonia. COVID-19 is either rare in children or it has not been diagnosed that often because this age group remain asymptomatic. The consequence is that children and younger adults who do not have underlying conditions, such as impaired lung function or immunosuppression, have a much lower risk of severe forms of COVID-19 than other age groups. Children also tend to have many viral infections and it is thus possible that repeated viral exposure supports the immune system when it responds to SARSCoV-2.**

Conclusion: **From the above and other immunological findings we show that children in school are safe enough from COVID-19, but those with underlying medical conditions would need close and constant monitoring.**

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) infection caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) emerged into a previously unexposed and presumably fully susceptible population at the end of 2019, facilitating its rapid spread around the world. Severe COVID-19 disease is characterised by three phases: the viral and pulmonary phases, followed by the final hyper inflammatory phase, which can lead to severe acute respiratory distress syndrome (ARDS), impaired cardiac function and death [1].

Several mitigating actions followed the scare of the pandemic and among them countries closed all their learning institutions. In Kenya, the closure has been for near the whole of year 2020. The virus initially slowed down but there has come a second and slightly more vicious wave. Learning institutions are fully opened and learning is ongoing in more or less similar circumstances as before the pandemic. Now after assessing how the virus affects various age groups, and from the immunological perspective, we agree to the opening of the schools for our children but with tough preventative measures in place and close monitoring of the children with underlying medical conditions that predispose to COVID-19 infections or worsening it. Teachers and other adults working with the children would need to practice all the measures used by other workers across the world. In this review we give our argument.

A general pattern has been reported from multiple countries indicating that children who test positive for COVID-19 experience a mild form of the disease [2]. This means that children and younger adults who do not have underlying conditions, such as impaired lung function or immunosuppression or other conditions like diabetes, have much lower risk of severe forms of COVID-19 than other older adults.

It has since been well documented that children with COVID-19 suffer a milder illness than adults, with better clinical outcomes overall. Age-specific case fatality ratios appear to increase continuously from close to 0% in children aged <10 years to about 13% in adults aged ⩾80 years [3]. Globally, children suffer the greatest burden of most infectious diseases, particularly respiratory infections; hence, the low burden of COVID-19 in children is viewed by many as surprising. Studies on corona virus have raised interesting questions in discussing the differences in COVID-19 morbidity and mortality between children and adults

From the perspective of the immune system, which is tasked with the body's defence against infections, there are a number of possible reasons to explain why children suffer less severe illness. These include but are not limited to age-related variation in angiotensin-converting enzyme (ACE) 2 receptor expression, trained immunity, and differences in lymphocyte and natural killer cell abundance among others as will be discussed below in this review. The key is the interaction between host immunological response and viral pathogenetic mechanisms.

The other reasons for the protection of lungs and airways against COVID-19 in children are non-immunological and they include lack of comorbidities, less exposure to particulate matter and pollutants, relative lack of physical and mental stress in children, among others. These will, however, not be discussed in this review.

Differences in the expression of the ACE 2 receptor

There is a cellular receptor known as angiotensin-converting enzyme 2 (ACE2) on human beings, which is used by SARS-CoV-2 virus to bind to the host cells and their subsequent infection [4]. This receptor is widely expressed in various organs and tissues including the airways, the lung and intestines, digestive tract, lung, kidney, heart

and blood vessels but more than 80% of total ACE2 expression is found in type II alveolar cells [5]. The S protein of the virus mediates viral attachment to the host ACE2 receptor and the subsequent fusion between the viral and host cell membranes is aided by transmembrane serine protease 2 (TMPRSS2) to allow the entry of viruses into the host cell [6].

Children have much smaller number of alveoli (hence fewer type 2 cells) compared with adults and since ACE2 and TMPSS2 are expressed on these cells, there is thus lower expression of ACE2 and TMPRSS2 in children which may spare them from excessive immune reaction compared with adults who have elevated ACE2 expression which could explain the worse outcomes in adults infected with SARS-CoV-2 compared to children [7].

In animal models, it has been demonstrated that increased amounts of this receptor in older rhesus monkeys makes them more susceptible to SARS-CoV than younger monkeys [8].

Age-related changes of the immune system

Immunosenescence (deterioration of the immune system brought on by natural age advancement) may also explain COVID-19 age variability. With aging, there is a gradual decrease of naïve T cell numbers due to thymic involution, shrinkage in the repertoire of T cell clones generated in the thymus, and loss of costimulatory receptor CD28 [9, 10,11,12]. There is also shortening of telomeres along with increased production of pro-inflammatory cytokines which is associated with impaired immune response to new antigens [13, 14]. Ageing thus leads to a progressive decline in the normal functioning of the immune system, which impairs a person's ability to respond to new stimulants and thus leads to weaker immune responses. This affects the number and function of the peripheral CD4 and CD8 T-cell pool and has a negative influence on the adaptive immunity leading to increased morbidity and mortality in the elderly [15]. In this regard, CD8 T cells appear to be more susceptible to age, exhibiting a stronger reduction in number and function compared with CD4 T cells. Since CD8 T cells have a fundamental role in viral disease control and the clinical outcomes of many viral infections (by recognizing and destroying virus-infected cells by cell lysis and producing toxic chemokines), this leads to faster progression of the COVID-19 disease among the elderly.

Differences in immune response

The adaptive immune response plays a crucial role in decreasing the effects of SARS-CoV-2 infection whereby pro-inflammatory mediators activate Th1-type immune response (CD4+ and CD8+ T cells) and B lymphocytes that cause an effective virus-specific antibody response [16]. It is also worth noting that studies focusing on adults infected by SARS-CoV-2, have reported much higher rates of lymphocytopenia (low number of lymphocytes) compared to children [17, 18, 19], especially those with severe disease, suggesting immune dysfunction [20, 21,22] and this has been associated with worse outcomes [23]. There is thus reduced potent antivirus T cell response in aged hosts which could lead to an exaggerated immune response and damage, which is not seen in children, since T cells are required for controlling exaggerated innate immune responses [24, 25].

In children with SARS-CoV-2, the numbers of peripheral blood lymphocytes remain mostly in the normal range, suggesting less immune dysfunction [26, 27]. Moreover, in healthy persons, lymphocytes, especially NK cells, are constitutionally in a greater amount in children than in adults [28, 29, 30], probably due to frequently experienced viral infections and vaccinations in childhood [31], resulting in frequent immune system activation in the first years of life. This would result in more effective

defence against different pathogens, including respiratory viral infections [32] such as COVID-19.

The Cytokine storm / Children have a less vigorous immune response

A strong immune response is a double-edged sword. It may help host cells to defeat the virus more efficiently but on the other hand, it can result in more cytokines being released from the immune cells (a "cytokine storm"), which is a key cause of the severe disease and death of COVID-19 patients by the exponential growth of inflammation, apoptosis and organ damage [33, 34]. The cytokine storm actually refers to the overproduction of inflammatory cytokines with a wide range of biological activity from a variety of tissues and cells (mainly immune cells), which is due to different infections and a loss of negative feedback on the immune system. When SARS-CoV-2 infects the body, the inflammatory response plays an antiviral role, but a strong cytokine storm due to an unbalanced response can be very damaging to the patients.

One possible explanation for the milder COVID-19 disease presentation in children is that compared to adults, children have a less vigorous immunological response to the SARS-CoV-2 virus. Children's immune systems are still developing, and an inadequate immune defence can prevent excessive host immune damage. In the recent COVID-19 infections, the proportion of children with COVID-19 with elevated inflammatory markers has reportedly been low [35] resulting in a less vigorous immune response to the virus than in adults.

The cytokine storm plays an important role in the pathogenesis of severe SARS-CoV-2 infections [36]. Several studies have shown that elevated inflammatory markers are less common in children and lymphocytopenia seemed rare, that there is a better prognosis in infected children than in adults and that fewer children seem to develop severe pneumonia [37]. The elderly may be at high risk from COVID-19 because of their overreaction to the viral infection causing the cytokine storm. In fact, patients with severe COVID-19 show systemic immune over reactivation which causes significant increases in cytokines such as IL-2, IL-7, IL-10, GSCF, IP10, MCP-1, MIP1A and TNF-α, characteristics of a cytokine storm [38]. In turn, these cytokines drive a positive feedback on other immune cells and continue to recruit them to the sites of inflammation, begetting the exponential growth of inflammation and organ damage. In short, it is the unceasing extreme activation and attack of the immune system. The main cytokines involved include interleukins (IL), interferons (IFN), tumour necrosis factor (TNF), colony stimulating factors (CSF), the chemokine family and growth factors (GF).

Trained immunity after previous exposures to other viruses and previous vaccines

Trained immunity is cross protection against various pathogens activated by some vaccines or by previous infections. Children undergo several viral infections and scheduled immunisations, which may boost their innate and adaptive immunity. Children thus have a variety of memory T-cells from frequent exposure to a variety of viruses and vaccinations in childhood, and it maybe that this cross-reacts with the SARS-CoV-2 virus and provides protection against infection. The presence of other viruses simultaneously infecting the mucosa of lungs and airways, which occurs commonly in young children, could also limit the growth of SARS-CoV-2 by direct virus-to-virus interactions and competition [39]. Trained immunity thus represents an immune memory after antigen exposure. Several studies have shown that children are more susceptible than adults to infection by Respiratory syncytial virus (RSV) and *Mycoplasma pneumoniae* (MP) [40, 41] and that antibodies against RSV and MP in the blood of children appear to offer cross

protection against SARS-CoV-2 infection [42, 43]. It is thought that these events may train the immunity of children due to neutralizing cross-reactive antibodies of MP and RSV which, being more common in children than in adults may protect against COVID-19 infection and thus result in better clinical response in children.

Bacillle Calmette-Guerin (BCG) vaccine has also been shown to offer cross protective immunity to COVID-19 thus reducing morbidity and mortality [44]. In this regard, countries without universal policies of BCG vaccination (e.g., USA, Italy) have been affected more severely as compared to countries with universal and long-standing BCG policies. Also, countries that have a late start to universal BCG vaccination (e.g., Iran in 1984) had a high mortality [45]. In vaccinated children, NK cells activation was still significantly elevated after 1 month of vaccination and protected against influenza and other respiratory viral infections [46]. Indirect epidemiological analyses also have suggested a protective role of the Measles, Mumps, and Rubella vaccine against COVID-19 [47]. However, after 10 years, the majority of vaccinated individuals did not have protective IgG titre against measles and this age-dependent decline in immunogenicity against measles vaccine could explain why there is higher occurrence of COVID-19 in adults [48].

The risk of paediatric multi-system inflammatory syndrome (PMIS)

Though children are relatively spared from the effects of COVID-19, there has been reported a hyperinflammatory syndrome with overlapping features of Kawasaki disease and toxic shock syndrome, and whose prevalence in children is between 1-3%. This condition referred to as Paediatric Inflammatory Multisystem Syndrome (PIMS), is temporally associated with SARS-CoV-2, especially in children of African and Asian descent. Affected children show raised inflammatory markers (e.g. CRP, ferritin, Troponin I, Creatinine Kinase and pro-BNP). The children also show diverse and non-specific symptoms which commonly include persistent fever, mucocutaneous involvement (hands and feet oedema, conjunctivitis, swollen and cracked red lips, rash), cardiac dysfunction (myocarditis, electric abnormalities, valvular dysfunction, shock, coronary aneurysms or dilatation), gastrointestinal symptoms, and lymphadenopathy [49,50]. The children show improvement after a short while and none of them have needed extracorporeal life support while most children recover from the condition.

PIMS is immunologically mediated and is a post-infectious process caused by non-neutralizing IgG antibody through antibody-dependent enhancement. Most patients (96%) more often have a positive test for antibody to SARS-CoV-2 than for the virus using nasopharyngeal RT-PCR thus supporting the evidence that PMIS might not be an acute COVID-19 infection, but it is more likely a post-immunological reaction [51]. The post-infectious mechanism rather than a direct viral strike for PMIS is further underlined by the fact that the onset of the condition happens between 3 and 6 weeks after COVID-19 peaks and decreases when COVD-19 cases decrease. This time shift, coupled with the low positivity rate of direct testing, suggest a post-infectious mechanism rather than a direct viral strike [52].

There is an ethnicity predisposition in PMIS showing that there is a higher proportion of African and Asian ancestry in children with this condition. African and Asian children in Europe and North America are thought to have earlier maturation of lung entry ports. Commensurately, the numbers of ACE 2 receptors, which are necessary receptors for SARS-CoV-2 spike protein attachment, are higher in these two ethnicities compared to the Caucasian. Consequently, more lung cells are infected, and when these cells are

destroyed, the spike proteins are released in large amounts and since these are highly immunogenic materials, they excite the immune system, culminating with an inflammatory storm. Furthermore, while in Europe and North America it is thought that these children are given an ethnically determined diet, which is a diet low in vitamin D, and hence could suffer relative vitamin D deficiency (vitamin D is known to play an active role in immune modulation). Thus, these factors makes them more susceptible to hyperinflammation [53].

It is important thus that pediatricians consider early aggressive treatment and close monitoring of children, in whom a severe COVID-19 disease course might be occurring, especially those children of African and Asian descent.

CONCLUSION

In summary, COVID-19 infection is a mild infection in children with no serious health consequences. It either manifests with mild symptoms or no symptoms at all. In fact, as part of the proof of this concept, and especially in Kenya, where children have been in school for the last four months, to the best of our knowledge, there have not been reported many serious cases of the disease and those that have been sick in schools have been said to have recovered. In conclusion, it is thus safe to have children in school during this period COVID-19 infection pandemic but those children with underlying medical conditions should continue being monitored for disease complications including conditions like PMIS. We also emphasize that there is need for continued use of recommended precautions to reduce spread of COVID-19.

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