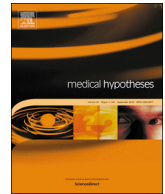




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# Understanding Covid and the associated post-infectious hyper-inflammatory state (PIMS-TS) in children

Shelley Riphagen

*Paediatric Intensive Care Unit, Evelina London Children's Hospital, Westminster Bridge Road, London SE1 7EH, United States*



## ABSTRACT

When SARS-CoV2 infection was first reported from China, very few children had severe lung or systemic disease. Approximately six weeks after the first adult cases were reported in the United Kingdom, a small subgroup of children of largely non-white backgrounds, presented with severe hyper-inflammatory disease, most likely associated with Covid. The possible reasons for this ethnic predilection are explored.

## Introduction/background

The SARS-Corona virus 2 (SARS-CoV2) affected human populations starting in China in December 2019 [1]. The first population reports in China, suggested children were not severely affected. That was not the lived experience for a small sub-group of children first described in the United Kingdom, then in Europe and North America. This group presented with a post infectious hyper-inflammatory state resulting in critical illness requiring the highest levels of paediatric intensive care support [2,3]. Notably in this group, Afro-Caribbean and Asian children were over represented in these case series.

## Hypothesis/theory

Afro-Caribbean children display an ethnically determined predisposition to hyper-inflammation, not commonly seen in Caucasian children, which predisposes them to severe SARS-CoV2 related disease. The specific points to this hypothesis are as follows

- Covid enters respiratory tract cells through Spike protein attachment to ACE2R
  - o Development of ACE2R is age dependent.
  - o ACE2R play important part in immune modulation
  - o Lung development occurs in stages and is dependent on developmental maturity. Black and Asian children mature earlier than Caucasian children
  - o As lungs mature ACE2R number increases
- African and Asian populations are genetically predisposed to hyper-inflammation
  - o The Corona virus spike protein is not destroyed by destruction of infected cells, and on destruction of infected cells the capsular spike protein is released in large amount. The spike protein is

highly immunogenic and sets up an inflammatory storm (similar to that seen with killing of bacteria with toxic glycoprotein containing outer layers eg meningococcus)

- In countries of origin, African and Asian population have higher sun exposure and higher Vit D levels
  - o Vit D has an anti-inflammatory role
  - o Vit D levels are lower in obese individuals
  - o Vit D levels are lower in African and Asian children in Europe and North America for two reasons: Lower sun exposure and ethnically determined, relatively low Vit D containing diet, without the Northern European and North American preference for dairy
- The above factors contribute to a "perfect Covid storm", setting up a subgroup of children for severe disease.

## Evaluation of hypothesis

Angiotensin converting enzyme 2 receptors (ACE2R) are surface proteins present on many epithelial cells including lungs, heart, blood vessels and other organs [4]. They are most abundant on epithelial cells of the nose, mouth and lungs especially on type 2 pneumocytes. ACE2 receptors are a vital element in the chemical pathways that control blood pressure, inflammation and wound healing by negative regulation of the renin angiotensin system. Expression of ACE2R is controlled by a 40 Kb gene on chromosome Xp22 with 18 exons. SARS-CoV2 uses membrane bound pulmonary ACE2 receptors to gain entry into cells. The SARS-CoV-2 major spike glycoprotein (S1) binds to the N-terminal region of ACE2, which then acts to open a "cellular doorway" for the virus [5]. Once SARS-CoV2 is bound to the ACE2 receptor, the infected cell cannot undertake its usual cellular role, and the virus uses the cellular apparatus for RNA replication, before the failing infected cell is shed.

ACE2 receptor expression in the nasal mucosa is age dependant,

*E-mail address:* [Shelley.riphagen@gstt.nhs.uk](mailto:Shelley.riphagen@gstt.nhs.uk).

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with children found to have significantly lower levels than adults [6]. Lung development in children is age dependent. After birth, it accelerates rapidly with main focus on alveolar multiplication until 2 years of life. It then continues linearly until about 10 years of age with growth hormone dependent elongation and enlargement, without addition, of lung units. After 10 years, with the onset of puberty, there is ongoing sex steroid dependent lung growth terminating at around age 20 years with fully mature lungs. An important note needs considering with regard to lung size at the end of development, is that there is about a 25% difference in lung size between men and women of identical height, which occurs during puberty primarily due to thoracic volume difference between sexes [7]. Although pulmonary ACE2 receptor number has not been measured during the different ages of childhood, it can only be concluded that as the lung unit number increases and enlarges, the number of pulmonary ACE2 receptors must increase, in line with what is seen with age dependant nasal epithelial ACE2 receptors, thus putting children at increasing risk of higher SARS CoV2 related disease burden as they progress through childhood.

From this basic knowledge, one could predict that children under 2 years of age will be largely unaffected by SARS CoV2 and that up till 10 years of life, the severity of disease related to viral load will be lower than in older children over 10 years. We can probably also predict that teenage boys and men will likely be more severely affected than girls and women.

What has been noted in general in children, is that SARS CoV2 lung disease is almost absent under 10 years. Between 10 and 20 years, there is an increasing number of children who become seriously unwell with SARS CoV2 related disease, in a delayed manner with a significant degree of hyper-inflammation with a predisposition for Afro-caribbean and Asian children [2,8,9]. What information is already known to try and understand these differences?

In the Millenium Cohort study, children of African and Asian heritage in the United Kingdom had earlier onset puberty and accelerated maturation compared with Caucasian children, even after socio-economic factors and adiposity were accounted for [10]. This maturation will include the lungs. The early onset of maturation may have provided population survival advantage in the countries of origin.

Ethnic differences in inflammation have been widely described in numerous settings and countries. Keloid formation, a benign fibroproliferative overgrowth or hyper-inflammatory response to skin injury is more common in dark skin than light skin, and thus much more common in African and Asian populations [11]. The exact genetic basis for this difference is not fully understood. There is good evidence that Afrocaribbean populations have an increased incidence of inflammatory disease in general and higher interleukin levels [12,13] than Caucasians with similar disease, when all other confounders, including socioeconomic factors, are accounted for. This difference manifests in children in the higher incidence of sub-glottic stenosis after croup requiring intubation in African American children [14]. The higher incidence of childhood asthma and wheezing in Afro-caribbean children in England, is only partly explained by socio-economic factors [15]. Non-white children with SLE and JIA are more likely to develop macrophage activation syndrome as an abnormal inflammatory response to immune trigger.

In Africa and Asia responding aggressively to an infectious trigger [17], which is the main cause of childhood mortality, would have provided survival advantage in childhood [16,17]. In the setting of bacterial and parasitic infections, this hyper-inflammatory, aggressive response would have brought infection under control, and the triggering stimulus would have subsided. Along with this are two other contributory factors to inflammation in this group of children, namely vitamin D levels and body mass index (BMI).

Historically in disease, return to health was associated with time spent in a sunny country for recuperation. Sunshine was positively associated with recovery from active TB and improved fracture and skin healing in trauma victims. Vitamin D related peptides released in

response to UVA and UVB light play an active role in immune modulation [17]. Supporting this, inflammatory diseases like multiple sclerosis are almost absent in sunny countries. Vitamin D levels from sunshine, acting as anti-inflammatory steroid in children in Africa, are higher than in African children in European countries and North America [18–21]. In Africa normal levels of vitamin D would have contributed to resolution of inflammation and healing, despite a culturally determined low Vit D diet in Africa and Asia, where dairy does not contribute highly to a normal family diet. For African and Asian children in Europe and North America, continuing to eat a largely low vitamin D content traditional diet, without the compensation of large amounts of sunshine, vitamin D deficiency will be more pronounced. Multiple studies in Europe have identified non-Caucasian immigrants in Europe as a high risk group for Vitamin D deficiency [21] Body mass index is directly linked to vitamin D levels in children and adolescents [22] and in general, children in Africa and Asia have a lower body mass index (BMI) than their counterparts in Europe and North America [23]. Higher BMI, across the ages, is associated with a continuous low grade pro-inflammatory state [24].

Taking this multisource acquired knowledge into account, it can be predicted that children of African and Asian backgrounds living in Europe and North America are more likely to respond in hyper-inflamed manner to an infectious trigger. This will be more pronounced if that infectious stimulus is not brought under control in a short period of time. Low vitamin D levels and higher BMI will both be contributory factors to the degree of inflammation and thus degree of illness seen. The effects will be more pronounced in older children and especially in boys.

## Conclusion

The "perfect Covid Storm" for severe disease, in the subgroup of African and Asian children in Europe and North America that has been demonstrated during this pandemic, has a number of associated factors.

With regards to disease attributable to Coronavirus (SARS CoV2) and its effects on children, it can be predicted that young children under 2 years of age will not be affected or extremely mildly affected due to low levels of cellular receptor entry ports. Disease burden will increase through childhood, with children over 10 years more severely affected. In Europe and North America, children with African and Asian backgrounds are likely to be more affected because of earlier developmental maturation including of lung entry ports, low levels of Vitamin D due to skin colour in sunshine poor regions, with consequential reduced anti-inflammatory effect, and higher incidence of high BMI with its pro-inflammatory effect and compounded by the association of further reduction of vitamin D levels in higher BMI groups.

Afro-Caribbean boys will be most severely affected, with post pubertal boys at higher risk than girls due to bigger lung surface area to let in pathogens, and because of ethnic tendency to hyper-inflammation. This hyper-inflammation is not adequately moderated by rapid source control (Spike protein on viral coat present even if virus replication can be controlled/ killed) and is compounded by low levels of Vitamin D due to a combination of low sunshine levels with dark skin, and diet poor in vitamin D in the presence of higher BMI.

The evidence that remains to be uncovered is firstly, whether the ethnic basis for the hyper-inflammation in African and Asian children has a specific genetic determinant, that may convey population survival advantage in Africa, much like that conveyed by HbS (Sickle trait), but that when present as HbSS and not in Africa, produces a significant disease burden. The clue for this hyper-inflammation may be linked to the genetics of secondary haemophagocytic lymphohistiocytosis. Secondly, there is a need to measure ACE2 receptors in children of all ages and developmental maturity to document mechanism of entry. Finally, the correlation of vitamin D levels and BMI either independently or as a composite, with inflammation and infection in critically ill children needs to be determined. If this correlation is

proven, would supplementation early in disease change outcome, or even more important would targeted vitamin D supplementation for this group reduce the incidence of inflammatory disease in general? This would be applicable as a public health measure across the ages.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110029>.

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