Vitamin D status of children with Paediatric Inflammatory Multisystem Syndrome Temporally associated with Severe acute respiratory syndrome coronavirus 2 (PIMS-TS)

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Running Title: Vitamin D status of children with PIMS-TS
Abbreviations:

- **MIS-C**: Multisystem inflammatory syndrome in children
- **PIMS-TS**: Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2
- **25OHD**: 25-hydroxyvitamin D
- **PICU**: Paediatric intensive care unit
- **COVID-19**: Coronavirus Disease 2019
- **BAME**: Black, Asian and Minority Ethnic
- **RCPCH**: Royal College of Paediatrics and Child Health
- **CDC**: Centers for Disease Control
- **NICE**: National Institute for Health and Care Excellence
- **RT-PCR**: Reverse transcriptase polymerase chain reaction
- **EQA**: External Quality Assurance
- **NEQAS**: National External Quality Assessment Service
- **NDNS**: National Diet and Nutrition Survey
- **ESR**: Erythrocyte Sedimentation Rate
- **CRP**: C-reactive protein
- **Health Research Authority (HRA)**
- **IOM**: Institute of Medicine
- **SACN**: Scientific Advisory Committee on Nutrition
- **LVEF**: Left ventricular ejection fraction
Abstract

Coronavirus disease 2019 (COVID-19), has caused mild illness in children, until the emergence of the novel hyperinflammatory condition PIMS-TS: Paediatric Inflammatory Multisystem Syndrome Temporally associated with Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). PIMS-TS is thought to be a post- SARS-CoV-2 immune dysregulation with excessive inflammatory cytokine release. We studied 25 hydroxyvitamin D (25OHD) concentrations in children with PIMS-TS, admitted to a tertiary paediatric hospital in the United Kingdom (U.K), due to its postulated role in cytokine regulation and immune response. Eighteen children [median (range) age 8.9 (0.3 to 14.6) years, male=10] met the case definition. Majority were of Black, Asian and Minority Ethnic (BAME) origin [89%, 16/18]. Positive SARS-CoV-2 IgG antibodies were present in 94% (17/18) and RNA by PCR in 6% (1/18). 72% of the cohort were vitamin D deficient (<30nmol/L). The mean 25OHD concentration was significantly lower when compared to the population mean from the 2015/16 National Diet and Nutrition Survey (children aged 4-10 years) [24 vs 54nmol/L (95% CI: -38.6, -19.7); p<0.001]. The PICU group had lower mean 25OHD concentrations compared to the non-PICU group, but this was not statistically significant [19.5 vs 31.9 nmol/L; p=0.11]. The higher susceptibility of BAME children to PIMS-TS and also vitamin D deficiency merits contemplation. Whilst any link between vitamin D deficiency and the severity of COVID-19 and related conditions including PIMS-TS requires further evidence, public health measures to improve vitamin D status of the U.K BAME population has been long overdue.

Keywords: COVID-19, PIMS-TS, MIS-C, PICU, SARS-CoV-2, Vitamin deficiency
INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused mild illness in the majority of children, with few severe cases requiring hospitalisation and very few deaths,\(^1\) a finding also reflected in data from our paediatric unit.\(^2\) However, since April 2020, there has been increasing numbers of children presenting with a hyperinflammatory condition described by the U.K Royal College of Paediatrics and Child Health (RCPCH) as Paediatric Inflammatory Multisystem Syndrome Temporally associated with Severe acute respiratory syndrome coronavirus 2 (PIMS-TS)\(^3\) and as Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 by the Centers for Disease Control (CDC)\(^4\) in the United States. PIMS-TS has overlapping features with other childhood inflammatory conditions such as Kawasaki disease, toxic shock syndrome and macrophage activation syndrome\(^5\) but remains a separate clinical entity with distinct cytokine profiles, including marked elevations in IL-6, IL-8 and IL-10. Recent studies suggest that PIMS-TS is a post-infectious hyperinflammatory syndrome with the putative cause being immune dysregulation by SARS-CoV-2, as evidenced by laboratory confirmation of preceding SARS-CoV-2 infection.\(^6\)

The influence of 25 hydroxyvitamin D (25OHD) in PIMS-TS is proposed to be through its well-established role in modulation of adaptive and innate immunity, including regulation of inflammatory cytokine release.\(^7\) 25OHD downregulates type 1 T cells and upregulates type 2 T cells by reducing production of pro-inflammatory cytokines (IL-6, IL-8 and IL-17) and increasing anti-inflammatory cytokines (IL-10)\(^8\) and this immunoregulatory action is postulated to be involved in PIMS-TS.

A handful of studies have evaluated the association between 25OHD levels and COVID-19 in adults which were recently summarised in the rapid NICE (National Institute for Health and Care Excellence) evidence summary.\(^10\) To date, no studies have reported the vitamin D status of children with COVID-19 or associated conditions. We report, for the first time, the vitamin D status of children with PIMS-TS admitted to a single tertiary paediatric hospital in the Midlands region of the United Kingdom (U.K).
AIMS
- Report 25OHD concentrations in children with PIMS-TS requiring hospitalisation
- Compare mean 25OHD concentrations in children with PIMS-TS and healthy paediatric population
- Compare 25OHD concentrations and inflammatory markers in children with severe illness with circulatory shock requiring paediatric intensive care unit support (PICU group) to children who experienced a less severe disease course (non-PICU group).

METHODS

Study design and participants:
We undertook a single-centre observational study of children admitted to Birmingham Children’s Hospital, Birmingham, UK with PIMS-TS, between 12th April and 25th June 2020. All children who met the RCPCH,^{(3)} CDC,^{(4)} and World Health Organisation^{(11)} case definitions of PIMS-TS as detailed in Box 1 were included. Samples for 25OHD concentrations were obtained at presentation in all children as part of diagnostic bloods as per RCPCH PIMS-TS protocol.

Ethics and consent:
The project was approved as service evaluation by our institution’s audit committee. Additionally, all parents/legal guardians provided signed informed consent for inclusion of de-identified data in this report. Research Ethics Committee or Health Research Authority (HRA) approval was not required as per the HRA assessment tool.

Data collection:
Epidemiological, clinical and laboratory data on all children with PIMS-TS was gathered from clinical notes and electronic health record systems. Ethnicity details were recorded in clinical systems in accordance with the Office of National Statistics classification.^{(12)}

Laboratory methods:
SARS-CoV-2 RNA was tested for using semi-quantitative reverse transcriptase polymerase chain reaction (RT-PCR) from the upper airway using combined nasopharyngeal swabs. Lower airway samples were used in invasively ventilated children.

Antibody assay to SARS-CoV-2 spike glycoprotein was undertaken using an ELISA test.
25OHD concentrations were measured by quantitative liquid chromatography tandem mass spectrometry (AB Sciex API4000 MS/MS’ analyser). The laboratory is subject to External Quality Assurance (EQA) and meets the requirement of the UK NEQAS (National External Quality Assessment Service) Vitamin D scheme. The inter and intra-assay CVs were <10%.

**Body mass index (BMI):**

Children with BMI centile > 98th were classed as obese and those between 91st-98th were classed as overweight, in accordance with the RCPCH guidelines. (13)

**Vitamin D status and reference 25OHD concentration data:**

Based on the Institute of Medicine (IOM) classification, (14) 25OHD concentrations below 50 nmol/L (20 ng/L) were classed as suboptimal. 25OHD concentrations below 30nmol/L (12ng/L) were deficient, above 50nmol/L were sufficient and 30- 50nmol/L were insufficient.

As the children were previously fit and well with no co-morbidities, 25OHD levels were compared to healthy population means. Reference 25OHD concentrations for healthy children were obtained from the nationally representative National Diet and Nutrition Survey (NDNS) data. (15-17)

**Statistical analysis:**

Descriptive statistics were used to describe the baseline characteristics and are reported as numbers (percentages), mean and standard deviation (SD) or median and range as appropriate.

A one sample t-test was used to compare the mean 25OHD concentrations in the study cohort to the paediatric population mean.

An independent t-test was used to compare normally distributed data [Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP)] and a Mann-Whitney U test to compare non-normally distributed data (25OHD concentrations) between PICU and non-PICU groups. A p value below 0.05 was considered significant. All analyses were performed using SPSS statistical software v25.0 (IBM, Armonk, NY).
RESULTS

Baseline characteristics

Eighteen children with a median (range) age of 8.9 (0.3 to 14.6) years met the case definition. The majority were males (n=10).

A high proportion of the cohort was of BAME background (89%, 16/18). Only two children were of white British ethnicity. Obesity was noted in 31% (5/16) of the cohort and overweight in 31% (5/16).

SARS-CoV-2 IgG antibodies were positive in 94% (17/18) and RNA by PCR was positive in 6% (1/18). There were no notable co-morbidities, such as liver disease, renal disease, immunodeficiency or other conditions predisposing to recurrent infections and none were on any regular medications.

There were no deaths in the study population.

Details of the clinical characteristics and management are presented in Table 1.

Vitamin D status

Based on the Institute of Medicine (IOM) classification,14 89% (16/18) had suboptimal 25OHD concentrations of whom 72% (13/18) had deficient levels and 17% (3/18) insufficient levels. Sufficient 25OHD concentrations were noted in only two individuals [11%, 2/18] who were both of white British ethnicity. None of the BAME children had sufficient 25OHD concentrations and 81% (13/16) had vitamin D deficiency. Three children (20%, 3/15) were on commercially available vitamin D supplements purchased over the counter. All children requiring PICU care had suboptimal 25OHD concentrations.

Based on the UK Scientific Advisory Committee on Nutrition (SACN) recommendations where 25OHD levels < 25 nmol/L are considered inadequate,18 nearly 67% (13/18) of the cohort were deficient.

Mean 25OHD concentrations

The mean (SD) 25OHD concentration of the whole cohort was 23.6 (15.8) nmol/L. The mean (SD) 25OHD concentration in the BAME cohort (n=16) was 19.0 (8.8) nmol/L and the white cohort (n=2) was 60.3 (6.6) nmol/L. 25OHD below 50 nmol/L (20 ng/L) is classed as suboptimal, below 30nmol/L (12ng/L) is classed as deficient and 30- 50nmol/L is insufficient.
The mean 25OHD concentrations of the whole cohort was significantly lower when compared to the 2014/15-2015/16 NDNS mean 25OHD for children (n=514, males=276) aged 4-10 years\(^{15}\) [24 vs 54 nmol/L (95% CI: -38.6,-19.7); p<0.001]. The mean 25OHD concentration in the BAME group was significantly lower when compared to the mean 25OHD in non-white children (4-18 years, n=99/1102) from the 1997-98 NDNS data\(^{16}\) [19 vs 32 nmol/L (95% CI: -17.6,-8.3); p<0.001].

**PICU vs Non-PICU group**

**PICU group:** The majority of patients presented with features of circulatory shock and required PICU care (67%, 12/18) for circulatory support. All children in the PICU group required inotropes/vasopressors, 33% (4/12) required invasive ventilation and 8% (1/12) required hemofiltration for renal failure. None of the children required extra corporeal membrane oxygenation. The median (range) 25OHD concentration in the group was 18.2 (7.8-38) nmol/L. All except two patients had vitamin D deficiency (25OHD < 30 nmol/L). The median (range) CRP was 226 (48-480) mg/L and ESR was 54 (12-170) mm/hour.

**Non-PICU group:** Approximately, a third of the study cohort (33%, 6/18) presented with milder disease features and did not require admission to PICU. The median (range) 25OHD concentration in the group was 23.5 (10.6-65.0) nmol/L. The median (range) CRP and ESR were 110 (42-152) mg/L and 67.8 (5-115) mm/hour respectively. There was no mortality in either group.

Investigations and management of PICU group vs non-PICU group are presented in Table 2.

When compared to the non-PICU group the PICU group had lower mean SD 25OHD concentrations (Figure 1) (31.9 23.8 vs 19.5 8.8 nmol/L respectively; p=0.5) but this was not statistically significant. The mean SD CRP in the PICU group was significantly higher than that in the non-PICU group (228.5 131.0 vs 101.7 45.0 mg/L respectively; p=0.03). The ESR in the PICU and non-PICU groups did not differ significantly (76.5 54.4 vs 67.8 36.0 mm/hr respectively; p=0.70).

**Cardiac function**

All PICU patients had abnormal (< 55%) left ventricular ejection fraction (LVEF) based on modified Simpson’s method. Severe impairment was recorded in 16% (2/12), 50% (6/12) had moderate impairment and 34% (4/12) mild impairment.

In the non-PICU group 50% (3/6) had normal LVEF and it was mildly impaired in 50% (3/6).
Echocardiogram in children with suboptimal 25OHD (16/18) showed normal coronaries in 31% (n=5), prominent coronaries in 63% (n=10) and fusiform dilatation in 6% (n=1). Children with sufficient 25OHD levels (2/18) had normal coronaries and LVEF and did not require PICU admission.

**DISCUSSION**

This is the first report detailing the vitamin D status of children with PIMS-TS requiring hospitalisation, highlighting the alarmingly high proportion of deficiency. PIMS-TS was predominant in children of BAME origin, with 81% being vitamin D deficient. A high proportion of the whole cohort (72%) and specifically PICU cohort (83%) were vitamin D deficient. Children with PIMS-TS had significantly lower mean 25OHD concentrations compared to nationally representative healthy white British and BAME children, however there was no association with disease severity.

Suboptimal vitamin D status has been reported in around 50% of critically ill children in a previous systematic review and meta-analysis.\(^9\) We however, noted suboptimal 25OHD levels in 100% of our PICU group, probably due to the higher proportion of BAME individuals. The limited NDNS data on BAME individuals in the UK also reports a higher proportion of vitamin D deficiency (42.9%; n = 63) in comparison to white children (15.0%, n = 448).\(^17\) It is noteworthy that all children of BAME origin with PIMS-TS had suboptimal vitamin D status. A higher prevalence of PIMS-TS with disproportionate number of intensive care admissions of children from BAME background has been reported in the U.K.\(^5,19\)

Similarly, hypocalcaemic complications of vitamin D deficiency\(^20\), including nutritional rickets\(^21\), are also 90 to 166 fold higher in UK Black and Asian children when compared to their white counterparts.\(^22\)

The increased risk of acute viral respiratory infections with vitamin D deficiency and the potential protective effects of supplementation has been extensively reported.\(^23\) Nonetheless, currently there remains insufficient evidence to recommend routine supplementation to prevent acute respiratory tract infections\(^24\) or COVID-19.\(^10\) Evidence on the link between 25OHD status and SARS-CoV-2 continues to emerge, with suggestion of an inverse relationship between circulating 25OHD levels and SARS-CoV2 positivity.\(^25\) The relevance of vitamin D as a modifiable risk factor in severe PIMS-TS due to its actions on unregulated cytokine response requires further consideration. Consistent evidence of PIMS-TS being mediated by amplified inflammatory responses to SARS-CoV-2 and the regulatory actions of
25OHD on pro-inflammatory cytokine signalling, further substantiates the possible role of 25OHD in PIMS-TS. This hypothesis is strengthened by the association of low 25OHD with Kawasaki Disease, a childhood inflammatory disease with which PIMS-TS shares considerable overlap. 25OHD levels in Kawasaki’s disease has previously been linked to coronary outcomes which may be of relevance in children affected with PIMS-TS. Given that nearly 14% of the UK population are of BAME origin and are at a high risk of vitamin D deficiency, ongoing evaluation of the putative link between ethnicity, severe COVID-19 and vitamin D deficiency is essential. Randomised controlled trials in the community would be required to establish a causative link between vitamin D deficiency and COVID-19.

There was no link between 25OHD concentrations and disease severity in our cohort, but our study was not adequately powered to evaluate such a relationship. There is currently insufficient evidence to recommend vitamin D for prevention or treatment of COVID-19 or related conditions. Nonetheless, the finding of widespread deficiency in the BAME population cannot be disregarded. Suboptimal vitamin D status in UK residents, especially its BAME residents is a long-standing problem which warrants intervention. Older children and adolescents where there is a higher prevalence of severe COVID-19 and PIMS-TS are also reported to be at a higher risk of vitamin D deficiency. A number of factors need addressing to improve the vitamin D status of the UK population. Firstly, the threshold for sufficiency in the UK is set as 25 nmol/L, whereas other institutes and consensus guidance regard levels > 50 nmol/L as sufficiency and < 30 nmol/L as deficiency. Secondly, the recommended vitamin D requirement for children > 1 year in the UK is lower (10 µg or 400 IU daily) than that supported by other evidence based guidance (15 µg or 600 IU daily). Thirdly, less than a third of this lower recommended intake is met through diet in UK children due to the lack of widespread mandatory food fortification. Last but not the least, the uptake of vitamin D supplements in UK infants and children is also very low at <20% due to poor policy implementation. Hence, the UK has a higher prevalence of vitamin D deficiency compared to other countries at comparable latitude with similar proportions of BAME population. Robust vitamin D supplementation of all high risk groups has no notable side effects and is a safe option irrespective of the link. At risk individuals should be reminded of the need for supplementation at each healthcare contact.
Our study was limited by the small sample size given the rarity of the condition. Nonetheless, the data provided is of paramount public health importance. The chronicity of vitamin D deficiency was not known due to the unavailability of parathyroid hormone levels and the concurrent presence of hypophosphatasemia related to the acute insult\(^{35}\). However, the proportion of population with deficiency reported here mirrors data from other studies of predominantly BAME populations; \(^{36,37}\) yet again highlighting the importance of supplementation of high risk individuals and adoption of long term strategies such as food fortification, as a cost-effective way of optimising population vitamin D status\(^{38}\).

**Conclusions:**
PIMS-TS has seen an over-representation of children from BAME background, who are also at greatest risk of vitamin D deficiency. In view of the high prevalence of vitamin D deficiency in our PIMS-TS cohort, we call for mandated, year-round vitamin D supplementation of all high-risk children and adolescents. Food fortification with vitamin D should be strongly considered as a long-term strategy.

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REFERENCES

1. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109(6):1088-1095. doi:10.1111/apa.15270

2. Kanthimathinathan HK, Dhesi A, Hartshorn S, et al. COVID-19: A UK Children’s Hospital Experience. Hosp Pediatr. 2020. doi:10.1542/hpeds.2020-000208

3. Royal College of Paediatrics and Child Health. Guidance - Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS). https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims. Published 2020.

4. Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). https://emergency.cdc.gov/han/2020/han00432.asp. Published 2020.

5. Whittaker E, Bamford A, Kenny J, et al. Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2. J Am Med Assoc. 2020;324(3):259-269. doi:10.1001/jama.2020.10369

6. Lee PY, Day-Lewis M, Henderson LA, et al. Distinct clinical and immunological features of SARS-COV-2-induced multisystem inflammatory syndrome in children. J Clin Invest. 2020. doi:10.1172/jci141113

7. Panfili FM, Roversi M, D'Argenio P, Rossi P, Cappa M, Fintini D. Possible role of vitamin D in Covid-19 infection in pediatric population. J Endocrinol Invest. 2021;44(1):27-35. doi:10.1007/s40618-020-01327-0

8. Daneshkhah A, Eshein A, Subramanian H, Roy HK, Backman V. The Role of Vitamin D in Suppressing Cytokine Storm in COVID-19 Patients and Associated Mortality. medRxiv. 2020:2020.04.08.20058578. doi:10.1101/2020.04.08.20058578

9. McNally JD, Nama N, O’Hearn K, et al. Vitamin D deficiency in critically ill children: A systematic review and meta-analysis. Crit Care. 2017:21(1):1-13. doi:10.1186/s13054-017-1875-y

10. National Institute for Health and care excellence. COVID-19 Rapid Evidence Summary: Vitamin D for COVID-19 [ES28].; 2020.
11. World Health Organisation. Multisystem inflammatory syndrome in children and adolescents with COVID-19. https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Published 2020.

12. Ethnicity in England and Wales. https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11. Published 2011.

13. Royal College of Paediatrics and Child Health. BMI Chart - RCPCH. https://www.rcpch.ac.uk/sites/default/files/2018-03/boys_and_girls_bmi_chart.pdf.

14. Ross AC, Manson JAE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. J Clin Endocrinol Metab. 2011;9(6):53-58. doi:10.1210/jc.2010-2704

15. Public Health England. Results of the National Diet and Nutrition Survey (NDNS) Rolling Programme for 2014 to 2015 and 2015 to 2016.; 2018. https://www.gov.uk/government/statistics/ndns-results-from-years-7-and-8-combined.

16. Absoud M, Cummins C, Lim MJ, Wassmer E, Shaw N. Prevalence and predictors of vitamin D insufficiency in children: A great britain population based study. PLoS One. 2011;6(7):6-11. doi:10.1371/journal.pone.0022179

17. Cashman, K D. Dowling KG. Vitamin D deficiency in Europe: pandemic? Am J Clin Nutr. 2016;103(4):1033-1044. doi:10.3945/ajcn.115.120873.Am

18. Scientific Advisory Committee on Nutrition. Vitamin D and Health 2016.; 2016. doi:10.1007/s00198-015-3440-3

19. Davies P, Evans C, Kanthimathinathan HK, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. Lancet Child Adolesc Heal. 2020;4(9):669-677. doi:10.1016/S2352-4642(20)30215-7

20. Basatemur E, Sutcliffe A. Incidence of hypocalcemic seizures due to vitamin D deficiency in children in the United Kingdom and Ireland. J Clin Endocrinol Metab. 2015;100(1):E91-E95. doi:10.1210/jc.2014-2773
21. Julies P, Lynn RM, Pall K, et al. Nutritional rickets under 16 years: UK surveillance results. *Arch Dis Child*. 2020. doi:10.1136/archdischild-2019-317934

22. Uday S, Höglér W. Response letter to Nutritional rickets under 16 years: UK surveillance results. Archives of Disease in Childhood. https://adc.bmj.com/content/105/6/587.responses#response-letter-to-nutritional-rickets-under-16-years-uk-surveillance-results. Published 2020.

23. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. *Br Med J*. 2017;356:i6583. doi:10.1136/bmj.i6583

24. Scientific Advisory Committee on Nutrition. *Rapid Review: Vitamin D and Acute Respiratory Tract Infections*.; 2020. https://app.box.com/s/g0ldpth1upfd7fw763ew3aqa3c0pyvky.

25. Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. *PLoS One*. 2020;15(9):e0239252. doi:10.1371/journal.pone.0239252

26. Stagi S, Rigante D, Lepri G, Matucci Cerinic M, Falcini F. Severe vitamin D deficiency in patients with Kawasaki disease: a potential role in the risk to develop heart vascular abnormalities? *Clin Rheumatol*. 2015;35(7):1865-1872. doi:10.1007/s10067-015-2970-6

27. Brown RA. Rapid response to: Is ethnicity linked to incidence or outcomes of covid-19? BAME Children at High Risk of PIMS-TS, a Covid-19 Kawasaki-Like Disease - Vitamin D, a Factor? – Testing and Data Urgently Required. *Br Med J*. 2020;369:m1548. https://www.bmj.com/content/369/bmj.m1548/rr-25.

28. Uday S, Höglér W. Prevention of rickets and osteomalacia in the UK: political action overdue. *Arch Dis Child*. 2018;103(9):901-906. doi:10.1136/archdischild-2018-314826

29. Bates B, Lennox A, Prentice A, et al. National Diet and Nutrition Survey: Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme. 2014;4:1-27. doi:2014051

30. Bivins R. “The English Disease” or “Asian Rickets”? Medical Responses to Postcolonial Immigration. *Bull Hist Med*. 2007;81(3):533-568.
31. Munns CF, Shaw N, Kiely M, et al. Global consensus recommendations on prevention and management of nutritional rickets. Horm Res Paediatr. 2016;85(2):83-106. doi:10.1159/000443136

32. Aguiar M, Andronis L, Pallan M, Högler W, Frew E. Preventing Vitamin D deficiency (VDD): A systematic review of economic evaluations. Eur J Public Health. 2017;27(2):292-301. doi:10.1093/eurpub/ckw270

33. Jessiman T, Cameron A, Wiggins M, Lucas PJ. A qualitative study of uptake of free vitamins in England. Arch Dis Child. 2013;98(8):587-591. doi:10.1136/archdischild-2013-303838

34. Uday S, Kongjonaj A, Aguiar M, Tulchinsky T, Högler W. Variations in infant and childhood Vitamin D supplementation programs across Europe and factors influencing adherence. Endocr Connect. 2017;6(8):667-675. doi:10.1530/EC-17-0193

35. McKiernan FE, Shrestha LK, Berg RL, Fuehrer J. Acute hypophosphatasemia. Osteoporos Int. 2014;25(2):519-523. doi:10.1007/s00198-013-2447-x

36. Das G, Crocombe S, McGrath M, Berry JL, Mughal MZ. Hypovitaminosis D among healthy adolescent girls attending an inner city school. Arch Dis Child. 2006;91(7):569-572. doi:10.1136/adc.2005.077974

37. Darling AL, Hart KH, MacDonald HM, et al. Vitamin D deficiency in UK South Asian Women of childbearing age: A comparative longitudinal investigation with UK Caucasian women. Osteoporos Int. 2013;24(2):477-488. doi:10.1007/s00198-012-1973-2

38. Aguiar M, Andronis L, Pallan M, Högler W, Frew E. The economic case for prevention of population vitamin D deficiency: a modelling study using data from England and Wales. Eur J Clin Nutr. 2019;74:825–833. doi:10.1038/s41430-019-0486-x
Figure 1: 25OHD concentrations in PICU and non-PICU groups (p=0.11)
### Box 1

**RCPCH case definition (3)**

1- A child or young person presenting with fever, evidence of inflammation (neutrophilia, elevated CRP, and lymphopenia) with evidence of single or multi-organ failure (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features that may include full or partial criteria for Kawasaki Disease AND

2- Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus AND

3- SARS-CoV-2-PCR testing may be positive or negative.

**CDC case definition (4)**

1- An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological AND

2- No plausible alternative diagnosis AND

3- Positive for current or recent SARS-Cov-2 infection by RT-PCR, serology or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

**WHO case definition (11)**

1- Children and adolescents 0–19 years of age with fever ≥ 3 days and two of the following:

- Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
- Hypotension or shock.
- Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
- Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
- Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain) AND
2- Elevated markers of inflammation such as ESR, C-reactive protein or procalcitonin AND

3- No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes AND

4- Evidence of COVID-19 (RT-PCR, antigen or serology positive), or likely contact with patients with COVID-19.
**TABLE 1:** Baseline characteristics, investigations and treatment of children presenting with Paediatric Multisystem Inflammatory Syndrome Temporally associated with multisystem inflammatory syndrome in children (PIMS-TS).

| Decim al age (years) | Gender | Ethnicity      | BMI$^6$ (centile) | Respiratory support | Treatment | LVEF$^7$ modified Simpson’s method | Laboratory results |
|----------------------|--------|---------------|-------------------|--------------------|-----------|-----------------------------------|-------------------|
|                      | F= fema le | M= Male       |                   | IV$^1$ /NIV$^2$ /HFNC$^3$ /O2$^4$ | IVIG$^5$, MP$^6$ |                                    | (Reference values, where applicable, are provided in the footnote) |
|                      |         |               |                   |                    |           | Sars-Cov-2                        | 25OHD$^8$ (nmol/l) | Bone profile$^9$ | Inflammatory markers$^{10}$ | Haemoglobin$^{11}$ |

| PICU                 |        |               |                   |                    |           |                                    |                   |                   |                      |                     |
|----------------------|--------|---------------|-------------------|--------------------|-----------|-----------------------------------|-------------------|-------------------|---------------------|---------------------|
| 14·5                 | F      | Black Caribbean | 18·5 (25$^{th}$-50$^{th}$) | O2                 | IVIG, MP | 43% PCR -ve IgG +ve | 19 Adj Ca 2·33 PO4 0·99 ALP 76 (50-150) | CRP 252 ESR 90 | 79                  |                     |
| 9·6                  | M      | Asian         | 20·7 (91$^{st}$-98$^{th}$) | HFNC, O2           | IVIG, MP | 50% PCR -ve IgG | 8·6 Adj Ca N/A* PO4 N/A ALP 144 (80-150) | CRP 208 ESR 33 | 68                  |                     |
| Age | Gender | Race | Temperature | Details | PCR-ve | IgG +ve | Adj Ca 2⁺⁴⁰ | PO4 1.67 | ALP 70 (80-330) | CRP | ESR | Notes |
|-----|--------|------|-------------|---------|--------|---------|------------|--------|-----------------|------|------|-------|
| 8.8 | F      | Black/African Caribbean | 22.7 (98th-99.6th) | HFNC, O2, IVIG, MP | 32% | PCR-ve IgG +ve | 7.8 | Adj Ca 2.40 | PO4 1.67 | ALP 70 (80-330) | CRP 422 | ESR 90 | 84 |
| 12.6 | F | Black/African Caribbean | 15.2 (2nd-9th) | None, IVIG | 42% | PCR-ve IgG +ve | 17.5 | Adj Ca 2.25 | PO4 1.08 | ALP 70 (80-330) | CRP 128 | ESR N/A | 94 |
| 12.7 | M | Mixed White/African | 19.8 (75th-91st) | O2, IVIG | 38% | PCR-ve IgG +ve | 18.8 | Adj Ca 2.24 | PO4 0.95 | ALP 76(90-290) | CRP 86 | ESR 30 | 104 |
| 5.3 | M | Mixed White/African | 17.9 (91st-98th) | IV, O2, IVIG | 50% | PCR-ve IgG +ve | 16.8 | Adj Ca 2.32 | PO4 1.44 | ALP 69 (80-330) | CRP 101 | ESR 105 | 67 |
| 10.7 | F | Black/African Caribbean | 32.3 (>99.6th) | IV, NIV, O2, IVIG, MP, Tocilizumab | 25% | PCR-ve IgG +ve | 21.3 | Adj Ca 2.54 | PO4 1.34 | ALP 79 (80-310) | CRP 480 | ESR 170 | 83 |
|   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|
| 8 | F | Black/African Caribbean | 19-9 (91-98th) | IV | IVIG, MP, Infliximab | 48% | PCR -ve IgG +ve | Adj Ca 2·37 PO4 1·06 ALP 95 (80-330) |
| 8 | F | Black/African Caribbean | 14·3 (9th-25th) | None | IVIG, MP | 50% | PCR -ve IgG +ve | Adj Ca 2·48 PO4 1·05 ALP 120(80-330) |
| 7·1 | M | Black/African Caribbean | 23·4 (98-99·6th) | HFNC, O2 | IVIG, Prednisolone | 42% | PCR -ve IgG +ve | Adj Ca 2·30 PO4 0·8 ALP 102 (80-330) |
| 8·0 | M | Asian | 14·7 (9th-25th) | HFNC | None | 28% | PCR -ve IgG +ve | Adj Ca 2·40 PO4 1·17 ALP 59 (80-330) |
| 7·0 | M | Asian | 13·9 (2nd-9th) | IV, HFNC | None | 49% | PCR -ve IgG +ve | Adj Ca 2·37 PO4 1·77 ALP 95(80-330) |

Non PICU
|   | F    | Race                  | Age (91st-98th) | Other Ethnicity | Treatment | PCR   | Adj Ca | CRP   | ESR   |
|---|------|-----------------------|-----------------|----------------|-----------|-------|--------|-------|-------|
| 13·5 | F    | Any other White/Romanian | 25·6 (91st-98th) | None | IVIG, MP | >55% | PCR-ve | Adj Ca 2·39 | CRP 128 | 83 |
| 7·7  | M    | Asian                 | 20·5 (98th-99th) | None | IVIG, MP | >55% | PCR-ve | Adj Ca 2·25 | CRP 138 | 93 |
| 9·7  | M    | Mixed-White/Africanian | 17·9 (91st-98th) | None | IVIG     | >55% | PCR+ve | Adj Ca 2·33 | CRP 42 | 76 |
| 0·6  | F    | White                 | Not available   | None | IVIG     | >55% | PCR-ve | Adj Ca 2·74 | CRP 92 | 89 |
| 13·2 | M    | White                 | 27·5 (98th-99th) | None | None     | >55% | PCR-ve | Adj Ca 2·48 | CRP 152 | 136 |
| 0·29 | M    | Black/African         | Not available   | None | None     | >55% | PCR-ve | Adj Ca 2·48 | CRP 58 | 82 |
| an | Caribbean available | ve IgG +ve | PO4 1·29 ALP 403 (80-330) | ESR 5 |
|----|---------------------|-----------|---------------------------|-------|

5 Body Mass Index Centile, RCPCH chart [<2nd centile - low BMI, >91st overweight, >98th obese, >99·6th severely obese]

1 Invasive ventilation, 2 Non-Invasive ventilation, 3 High Flow Nasal Cannula oxygen, 4 Supplemental oxygen, 5 Intravenous Immunoglobulin, 6 Methylprednisolone

7 Left Ventricular Ejection Fraction [Mild impairment 45-54%, Moderate 30-44% and Severe <30%]

8 25-hydroxyvitamin D [deficiency < 30nmol/L, insufficiency 30-50 nmol/L, sufficiency >50 nmol/L]

9 Adjusted calcium (normal range 2·20-2·70mmol/L), Phosphate 1·30-2·40 mmol/L, Alkaline phosphatase (age and sex specific ranges provided in the table), * Not Available

10 C-Reactive Protein (normal range 0-10 mg/L), Erythrocyte Sedimentation rate (normal range 0 - 9 mm/hr)

11 Haemoglobin (reference range 3 months – 4 years: 110 - 140 g/L, 5 – 12 years: 115 - 140 g/L)
**TABLE 2**: Investigations and management of PICU group vs non-PICU group

| Investigation                                | PICU          | non-PICU       |
|----------------------------------------------|---------------|---------------|
| 25OHD\(^1\) median (range)                  | 18.2 (7.8-38) | 23.5 (10.6-65) |
| CRP\(^2\) median (range)                    | 226 (48-480)  | 110 (42-152)  |
| ESR\(^3\) median (range)                    | 54 (12-170)   | 67.8 (5-115)  |
| Inotropes/vasopressors n (%)                 | 12 (100)      | 0 (0)         |
| Invasive ventilation n (%)                   | 4 (33)        | 0 (0)         |
| Hemofiltration n (%)                         | 1 (8)         | 0 (0)         |
| LVEF\(^4\) normal n (%)                     | 0 (0)         | 3 (50)        |
| LVEF mild impairment n (%)                   | 4 (34)        | 3 (50)        |
| LVEF moderate impairment n (%)               | 6 (50)        | 0 (0)         |
| LVEF severe impairment n (%)                 | 2 (16)        | 0 (0)         |

\(^1\) 25-hydroxyvitamin D [deficiency < 30nmol/L, insufficiency 30-50 nmol/L, sufficiency >50 nmol/L]

\(^2\) C-Reactive Protein (normal range 0-10 mg/L)

\(^3\) Erythrocyte Sedimentation rate (normal range 0 - 9 mm/hr)

\(^4\) Left Ventricular Ejection Fraction [Mild impairment 45-54%, Moderate 30-44% and Severe <30%]