Can the immune system generate an appropriate response to SARS-CoV-2?

What is an appropriate immune response?

- **An appropriate immune response is one which:**
  - Recognises the virus as a pathogen
  - Delivers an immune response which is adequate to prevent severe disease or death
  - Does not result in complications such as excessive inflammation
  - Develops immune memory to prevent reinfection.
- But no studies have set out to test this specifically, so I investigated the **immune response associated with mild or asymptomatic COVID compared to severe or fatal COVID.**

Definitions of mild and severe COVID

- One problem is that **although there were WHO definitions of mild and severe COVID, few studies claim to have followed them.**
- So I am forced to accept the **researchers' categorisations.**
- I'm only considering **studies which showed statistically significant differences between mild and severe patients.** A number of early studies did not look at this statistical significance.
- My results show **a clear and distinct immune signature associated with mild compared with severe COVID.**
- I am **assuming that the immune response determines the severity of the COVID infection.** This may be an invalid assumption, although I have not found anything to suggest that it is so.

Does the innate immune system recognise SARS-CoV-2 as a pathogen?

- **Yes, through the pattern recognition receptors (PRRs). These are more highly upregulated in mild vs severe COVID.**
- After release into the cytoplasm, the single strand (ss) RNA viral genome of SARS-CoV-2 forms double-stranded (ds) RNA as an intermediate state prior to replication. Both ssRNA and dsRNA act as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which are recognised by host cell surface, endosomal and cytosolic pathogen recognition receptors (PRRs).
- Several PRRs (including Toll-like receptors (TLRs), retinoic acid-inducible gene-I (RIG-I) receptors (RLRs), and C-type lectin receptors (CLRs)) have been shown to activate their signalling pathways in response to SARS-CoV-2, triggering secretion of interferons and other pro-inflammatory cytokines.
- Two studies found that certain PRRs were more highly upregulated in asymptomatic or mild patients, compared to severe patients, with greater induction of type 1 IFNs.

Can the innate immune system generate a response to SARS-CoV-2 which differs between mild and severe COVID?

- **Pro-inflammatory cytokines,** chemokines, C reactive protein (CRP) and inflammatory mediators:
  - **Blood: Lower levels in mild vs severe patients – meta-analyses, reviews, studies**
  - **Respiratory system: Higher levels of certain cytokines in mild vs severe patients - studies**
- Granulocytes: lower percentage of granulocytes and lower granulocyte colony stimulating factor (G-CSF) in mild vs severe patients – reviews, studies
- Monocytes: studies divided over whether higher or lower in mild vs severe patients but agreed on dysregulation – meta-analyses, reviews, studies
- Macrophages:
  - Blood: rarely tested
  - Respiratory system: decreased lung pro-inflammatory (M1) macrophages but higher anti-inflammatory (M2) lung macrophages in mild vs severe patients. Macrophage activation syndrome correlated with mortality – meta-analysis, reviews, studies
- Neutrophils: lower levels in mild vs severe patients in blood and nasopharyngeal mucosa – meta-analyses, reviews, studies
- Natural killer (NK) cells:
  - Blood: higher levels in mild vs severe patients – meta-analyses, reviews, studies
  - Respiratory system: lower levels in mild vs severe patients - reviews

Pro-inflammatory cytokines: differences between mild and severe COVID

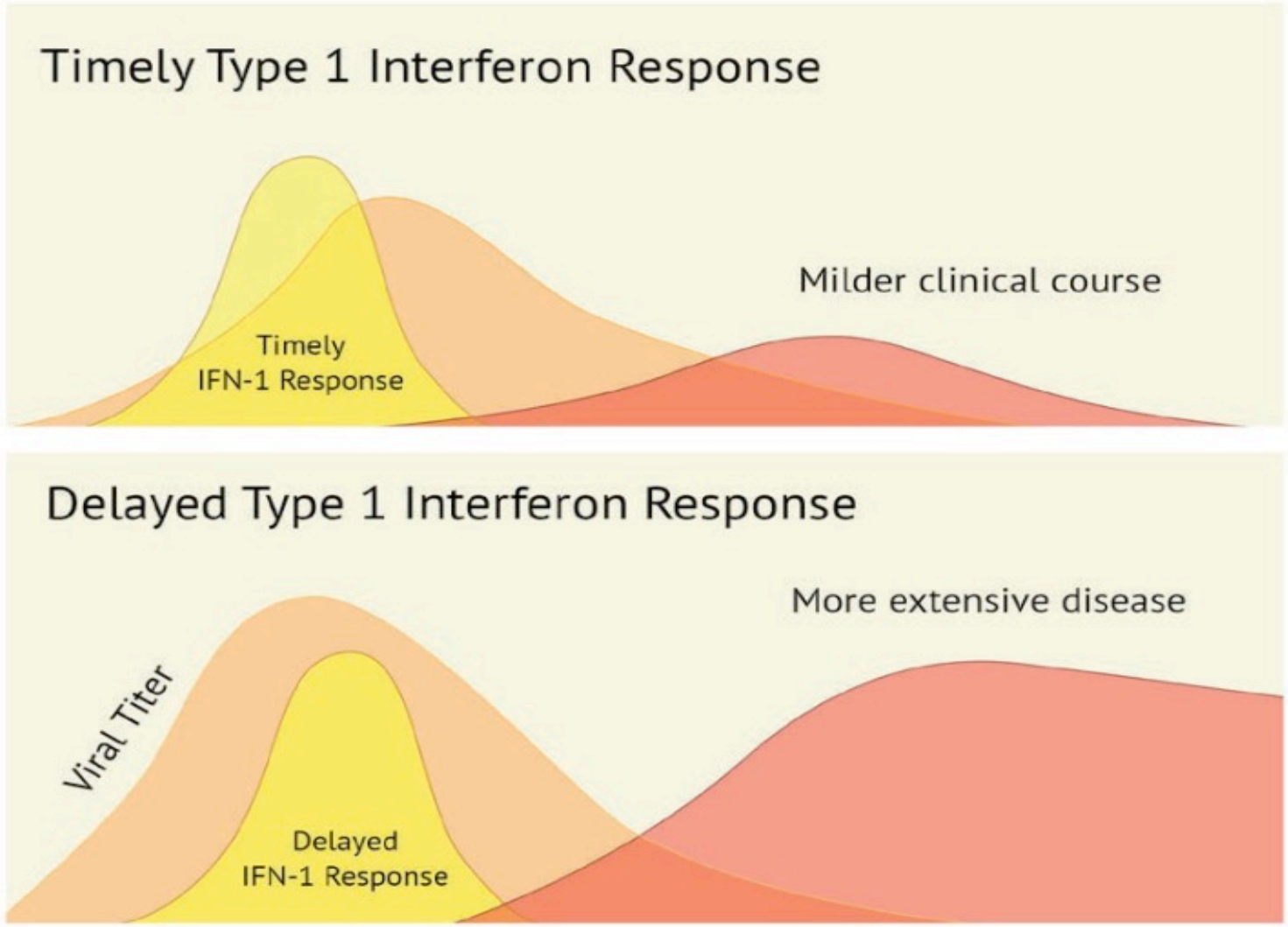
- **The data (including meta-analyses) suggest that mild infections are associated with active early cytokine production; in severe COVID the innate immune response is initially suppressed and delayed but later generates hyperinflammation.**
- **In mild disease, there is a short sharp burst of pro-inflammatory cytokines, followed by cessation of production and increased anti-inflammatory cytokines to calm the inflammation.**
- **In severe COVID, patient can be left with sustained and/or systemic inflammation, as seen in COVID complications.**
- It is thought that **the risk factors for severe COVID (ageing, obesity and type 2 diabetes) are due to the patients' pre-existing inflammatory state and dysregulated innate and adaptive immune responses;** the term 'inflammageing' has long described the inflammation of ageing.
- The prominent cytokine in severe COVID is interleukin 6 (IL-6) and is associated with viral load in critical patients. Elevated IL-6 can predict development of acute respiratory distress syndrome (ARDS) and contribute to lung-centric coagulopathy and increased haematopoiesis.

Interferons (a specialist type of cytokine): differences between mild and severe COVID-19

- **In mild COVID, there is a robust early production of type I and III interferons (IFNs) in blood and upper airways. In severe COVID, these responses may be delayed followed by hyperactivation, as well as elevated type II IFN-γ.**
- **High levels of autoantibodies against type 1 IFNs have been found in severe but not mild patients.**
- **Numerous studies report that not enough is understood about interferons** in general, or in the context of COVID-19.

- Studies of Middle Eastern Respiratory Syndrome (MERS) and respiratory syncytial virus (RSV) indicate that the timing of type I IFN production affects the cellular response.
- In severe disease, serum type I and type III IFN responses are often delayed or impaired, with increased accumulation of inflammatory monocytes and macrophages, resulting in immunopathology. Similarly, in the upper respiratory tract and lungs, patients with severe COVID-19 had lower activation of interferon signalling pathways.
- In severe and critical patients, absent IFN-β and low IFN-α production and activity (both type 1 interferons) and elevated type II IFN-γ were associated with a persistent blood viral load and an exacerbated inflammatory response.
- However, later in severe disease there may be sustained high levels of type I IFN, which drive inflammation-mediated lung tissue damage by increasing influx of inflammatory innate immune cells and inducing transcription factor NFκB, leading to an increase in TNFα and IL-6. Persistent type 1 IFN-α responses resulted in T cell exhaustion and the absence of NK cell responses and is associated with poorer clinical outcomes.
- In mild disease, there is a coordinated pattern of expression of interferon-stimulated genes (ISGs), whereas in patients with severe disease, these ISG-expressing cells are either absent or the response is delayed. This may be due to the increased antibodies in severe patients that functionally block the production of the ISG-expressing cells.

Pictorial representation of prompt and delayed type I IFN response



- A timely type 1 IFN response yields an antiviral response more likely to suppress viral burden, leading to a milder clinical disease course.
- A delayed innate immune response, including delayed upregulation of type 1 IFNs, may allow greater viral proliferation, leading to more extensive disease and poorer clinical outcomes.

(Yanuck SF, et al. Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery. Integr Med (Encinitas). 2020;19(Suppl 1):8-35)

Can the adaptive immune system generate a response to SARS-CoV-2 which differs between mild and severe COVID?

- **B cells:** **Higher blood count in mild vs severe patients – 4 x meta-analyses**
- **Serum (blood) antibodies** (see next slide): principally IgG and IgA
  - Neutralising: **Lower in mild vs severe – studies**
  - Binding: **Lower in mild vs severe – studies**
  - General: Mild vs severe patients show greater diversity, antibody class switching and affinity maturation - **meta-analysis, reviews, studies**
- **T cells** – the heavy-lifters in fighting viruses:
  - **In blood**: Higher numbers of T cells in mild vs severe patients and survivors vs non-survivors – **5 meta-analyses, reviews, studies**
  - **In lungs or respiratory tract**: higher numbers of T cells in mild vs severe patients; higher in survivors vs non-survivors – **review, studies**
- These results appear to be counter-intuitive for some and may be the cause of a lot of the misunderstandings about COVID immunity and antibodies, in particular.

Neutralising and non-neutralising antibodies

- **Neutralising antibodies bind to cell receptors to prevent the virus from entering and infecting human cells.** Neutralising antibodies can directly protect against the virus and decrease infection.
- **Non-neutralising (binding) antibodies bind to the virus and activate other immune system cells to destroy the virus but do not neutralise the virus.** They merely indicate to the immune system that the individual has been exposed to the virus or the vaccine but do not necessarily provide any protection in themselves.
- It was not until November 2020 that the US U.S. Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for an antibody test specifically looking at neutralising antibodies. (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-test-detects-neutralizing-antibodies-recent-or)
- In the UK and possibly elsewhere it seems that in testing, we have not differentiated between neutralising and non-neutralising antibodies.

Adaptive immune system: characteristics of mild COVID

- **Smooth innate-to-adaptive switching, with an early synchronised T and B cell response.**
- **Generally higher blood B and T cells but antibodies (binding and neutralising) are lower or may be absent.** Despite manufacturing antibodies, there is little correlation between B cell and antibody levels.
- Higher blood and respiratory system CD8+ cytotoxic T lymphocytes (CTLs), CD4+ T cells, T follicular helper cells (TFH), regulatory T cells (Tregs) and γδ T cells.
- **In the respiratory tract, IgG antibodies are higher in severe patients but IgA is higher in mild patients. IgA is the antibody of choice in COVID-19, as it largely resides in the mucous membranes, which lines the respiratory tract,** amongst other locations.
- **T cells may be induced within the first 7 days in mild patients. A potent response can be induced even with absent antibodies.**
- **Mild patients have a lower neutrophil to lymphocyte ratio (NLR),** a higher lymphocyte to monocyte ratio, a higher lymphocyte to cytokine ratio and a lower CD4+T/CD8+T cell ratio. **A high NLR was the most accurate predictor of progression to severe COVID.**
- Higher circulating T follicular helper (TFH) cells, meaning that most B cells are manufactured in germinal centres and are more able to produce neutralising antibodies, which can block the binding of the SARS-CoV-2 spike protein with its receptors, such as ACE2 (angiotensin converting enzyme 2), so preventing entry into the cells.

Adaptive immune system: characteristics of severe COVID

- There is **impaired innate-to-adaptive switching** i.e. innate immune cells (macrophages, monocytes, neutrophils and dendritic cells) fail to produce the cytokines, including Type I and III IFNs, that activate the adaptive immune response.
- There are regular reports of **lymphopaenia/lymphocytopaenia (low B and T cell levels),** particularly in the elderly and patients with ARDS. There are reports of **T cell exhaustion or depleted but hyperactivated T cells**, also seen in SARS-CoV-1 and influenza. T cell exhaustion is sometimes described as 'immune paralysis'.
- **There are high levels of total, neutralising and non-neutralising (binding) antibodies. Alternatively, production may be delayed or absent.**
- Severe disease is characterised by a CD4:CD8 T cell ratio (i.e. ratio of helper T cells to cytotoxic T lymphocytes) of ≥ 2.63.
- A higher frequency of plasmablasts (antibody-secreting cells) is produced through extrafollicular B cell activation (i.e. outside the germinal centre), which may trigger the large antibody production observed in patients with severe disease. This is likely due to the hyperactivation of pro-inflammatory cytokines from the innate immune system, which can impair and disrupt germinal centre formation and induces extra-follicular B cell activation.
- These antibodies are non-neutralising and are unable to clear the virus directly.

SARS-CoV-2 immune evasion (immune escape)

- **'Immune evasion/escape' occurs when the human host is no longer able to recognise and eliminate or neutralise a pathogen.**
- **This is because the pathogen has evolved strategies to hijack immune responses to facilitate infection and escape immune surveillance.**
- **SARS-CoV-2 seems to be more effective at this than other coronaviruses.**
- Certain variants are more prone to immune escape, particularly mutations in the receptor binding domain (RBD) region and other elements of the spike-glycoprotein.

SARS-CoV-2 immune evasion/escape: mechanisms

- Shielding viral RNA from pattern recognition receptors (PRRs) and interfering with their signalling pathways to suppress innate immunity, while facilitating viral RNA processing, maturation and subsequent translation.
- Downregulating MHC class I and II molecules and APC pathways, leading to inhibition of T cell-mediated immune responses. This ability may be enhanced in Omicron variants.
- Cytokine-related immune escape, particularly by inhibiting the production and signalling of type 1 and type III interferons (IFNs) and the activation of interferon-stimulated genes (ISGs) to allow unchecked viral replication and downregulation of adaptive immune system.
- Delaying macrophage activation or infecting and killing macrophages, neutrophils and dendritic cells.
- NLRP3 inflammasome-associated immune evasion.
- Suppressing natural killer cells and B cells and generating autoantibodies to B cells.
- Mutating its epitopes to evade neutralising antibodies and CD8+ T cells, particularly with Omicron.
- Using antibody-dependent enhancement (ADE) to aid survival by using the host's antibodies inside the immune cell in order to destroy the cell.
- Impairing autophagy, which prevents the body from clearing out infected cells.

Children: COVID incidence and severity

- **Children and adolescents have lower COVID infection rates and lower incidence of severe COVID compared to adults;** children aged 6-13 years are frequently asymptomatic. COVID is milder in children than influenza A.
- A meta-analysis carried out by Imperial College found that most children experience clinically mild disease or remain asymptomatically infected.
- A meta-analysis found that severe COVID-19 was present in 5.1% of children with comorbidities and in 0.2% without comorbidities. Childhood obesity was associated with severe COVID, with a relative risk ratio of 2.87.
- In Icelandic population screening, no child under 10 years of age had a positive COVID test result.
- There was a very low incidence of severe illness due to COVID-19 among Swedish children, even though day-care centres and primary schools remained open. From March to June 2020, a total of 15 children with Covid-19 were admitted to an ICU, 4 of whom had an underlying condition; no child with Covid-19 died.
- A 2022 German study found that among children aged 5-11 without comorbidities, the ICU admission rate was 0.0037% and a case fatality rate could not be calculated due to the absence of fatalities.
- In the US, relatively few children with COVID-19 are hospitalised and fewer children than adults experience fever, cough or shortness of breath.

What about children's viral load?

- A large Dutch pre-print study found that **children aged <12 years had significantly lower viral load than was found in adults.**
- Compared with the over-80s, they had 1/16th of the viral load.

(Euser S, et al. SARS-CoV-2 viral-load distribution reveals that viral loads increase with age: a retrospective cross-sectional cohort study. Int J Epidemiol. 2022 Jan 6;50(6):1795-1803)

https://www.dailymail.co.uk/sciencetech/article-9160303/Children-infected-coronavirus-viral-load-16-TIMES-smaller-80s.html

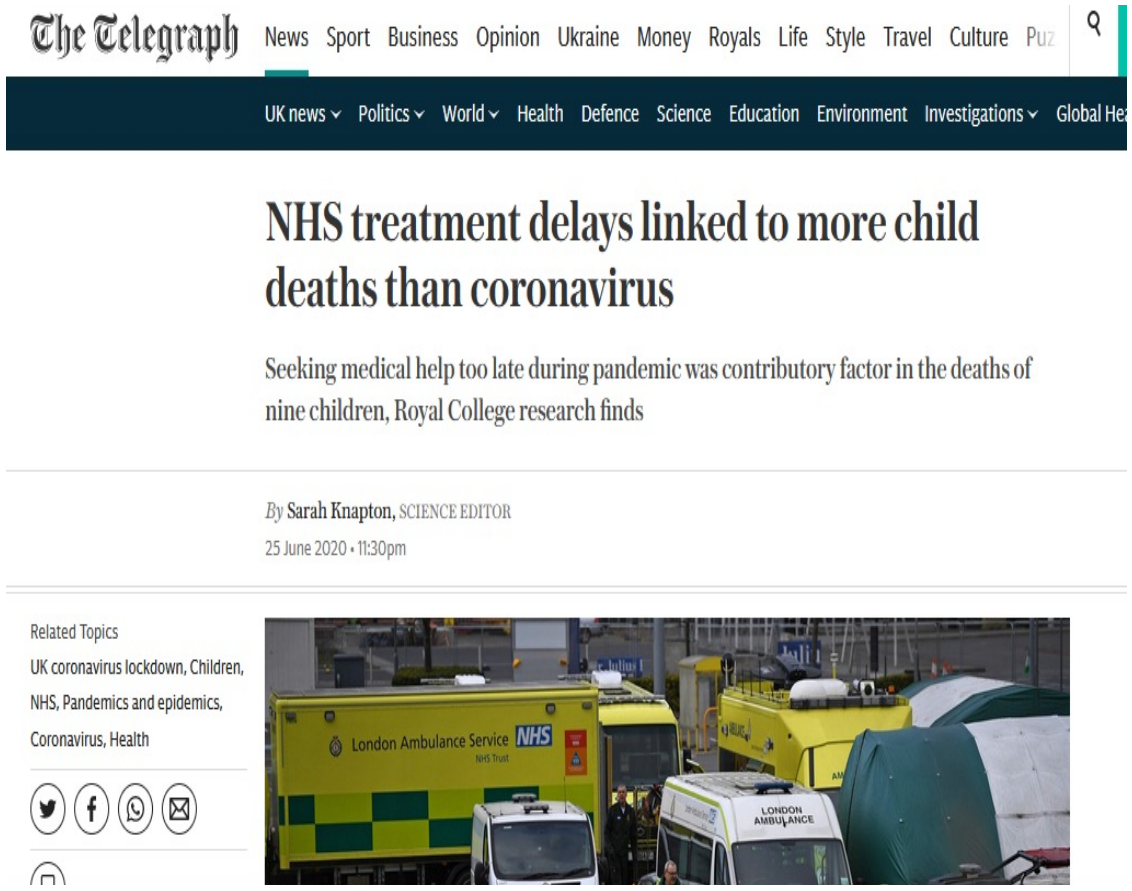
Children in the UK

- **Between January and May 2020, children represented 1.1% of COVID-positive cases, accounting for a very small proportion of confirmed cases despite the large numbers of children tested.**
- **There was no evidence of excess mortality in children.**
- Of the 1 million schoolchildren sent home and forced to self-isolate for 10 days during a school term, only 1.6% developed Covid. This finding came in summer 2021 when almost 1:4 schoolchildren were off school.
- Another study showed that mortality rate among children aged <18 years to February 2021 was 0.0002%; c.f 0.0003% in Ioannidis study for children aged <19 years.
- **Among those few who died, 64% had multiple comorbidities and 60% had life-limiting conditions.**

(Ladhani SN, et al. COVID-19 in children: analysis of the first pandemic peak in England. Arch Dis Child. 2020 Dec;105(12):1180-1185)

https://www.bbc.co.uk/news/health-57766717

Treatment delays cause more children's deaths than COVID



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NHS treatment delays linked to more child deaths than coronavirus

Seeking medical help too late during pandemic was contributory factor in the deaths of nine children, Royal College research finds

By Sarah Knapton, SCIENCE EDITOR

25 June 2020 • 11:30pm

Related Topics

UK coronavirus lockdown, Children, NHS, Pandemics and epidemics, Coronavirus, Health

- The Telegraph quoted a survey by the Royal College of Paediatrics and Child Health (RCPCH): **'More children died after failing to get timely medical treatment during lockdown than lost their lives because of coronavirus'.**
- Experts said the Government's "Stay Home, protect the NHS" message had made parents anxious about taking their children to hospital.
- Nine children died of cancer, sepsis (blood poisoning) and metabolic disease in the fortnight before the survey.

Why is COVID less prevalent and severe in children?

- The ACE2 receptor is reduced in the respiratory tract in children, allowing fewer points of entry. This is because many receptors are regulated by sex hormones and/or the immune system, both of which are immature in children.
- Children displayed higher expression of pattern recognition receptors in upper airway epithelial cells, macrophages and dendritic cells, resulting in stronger and earlier innate antiviral responses than in adults.
- Although children generally produce lower levels of inflammatory cytokines, they display higher expression of genes associated with IFN signalling. In nasal fluid they had higher levels of type 1 IFNs, IFN-γ and several interleukins compared to adults and serum concentrations of IFN-γ and IL-17A were higher in children compared with adults. This suggests a more vigorous early mucosal immune response in children compared with adults. And it is the early immune response that is critical.
- Compared to adults, children demonstrate markedly greater upper airway upregulation of pathways related to B cell and T cell activation and proinflammatory cytokine signalling, which likely contributes to protection from severe disease in the lower airway.
- Serum neutralising antibody titres remained low but T cell responses were >2x as high in children vs adults and were detected in many seronegative children.
- T cell cross-reactivity to other coronaviruses is established in early childhood but declines with age. Children's immune systems also show good cross-reactivity for variants.

The WHO does not acknowledge the low risk to children until 2023

- In spring 2023, the **WHO finally admitted that children are at very low risk of contracting COVID.**
- However, **they arrived at this conclusion not by following the science but because they needed to prioritise vaccines recipients:**
- 'The roadmap newly considers the cost-effectiveness of COVID-19 vaccination for those at lower risk – namely healthy children and adolescents – compared to other health interventions…..Countries should consider their specific context in deciding whether to continue vaccinating low risk groups, like healthy children and adolescents.'

(https://www.who.int/news/item/28-03-2023-sage-updates-covid-19-vaccination-guidance)

Other biomarkers of mild vs severe COVID

Higher in severe vs mild patients:

- Procalcitonin (PCT)
- Serum amyloid A
- Hepatocyte growth factor (HGF)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma glutamyl transpeptidase (GGT)
- Lactate dehydrogenase (LDH)
- Creatinine
- CK-MB isoenzyme
- Erythrocyte sedimentation rate (ESR)
- Ferritin
- Fibrosis index
- Macrophage colony-stimulating factor (M-CSF)
- Calprotectin
- Anti-phospholipid antibodies
- Galectin
- Troponin
- D-dimer
- Pulmonary surfactant levels, indicating increased permeability of the alveolar-capillary barrier
- Activated partial thromboplastin time and prothrombin time
- Fibrin degradation products
- Fibroblast growth factor (FGF)
- Platelet-derived growth factor-BB (PDGF-BB)
- IFN-γ-inducible protein 10
- C-reactive protein (CRP)

Lower in severe vs mild patients:

- Platelets
- Albumin
- Irisin
- Leptin
- Platelet-derived growth factor (PDGF)
- Calcium

Intestinal microbiome: faecal samples or rectal swabs

- **There was an inverse association between disease severity and bacterial diversity,** particularly lower abundance of Bifidobacterium, Faecalibacterium and Roseburium, while having increased Bacteroides (Hazan S, et al. Lost microbes of COVID-19: Bifidobacterium, Faecalibacterium depletion and decreased microbiome diversity associated with SARS-CoV-2 infection severity. BMJ Open Gastroenterol. 2022 Apr;9(1):e000871).
- Gut microbiota assessed from rectal swabs on hospital admission showed that those with severe disease had a significantly greater proportion of Campylobacterota and Actinobacteriota (Mazzarelli A, et al. Gut microbiota composition in COVID-19 hospitalized patients with mild or severe symptoms. Front Microbiol. 2022 Dec 6;13:1049215).
- High levels of gut bacteria of the Firmicutes phylum, especially Coprobacillus, Clostridium ramosum and C. hathewayi, but low levels of Faecalibacterium were associated with severe vs mild COVID (Yamamoto S, et al. The human microbiome and COVID-19: A systematic review. PLoS One. 2021 Jun 23;16(6):e0253293).
- In hospitalised patients, progression of respiratory failure leading to mechanical ventilation and mortality were associated with increased representation of Proteobacteria in the faecal microbiota and decreased concentrations of faecal secondary bile acids and desaminotyrosine (DAT) (Stutz MR, et al. Immunomodulatory fecal metabolites are associated with mortality in COVID-19 patients with respiratory failure. Nat Commun 13, 6615 (2022)).

Appropriate immune response: summary

- Pattern recognition receptors (PRRs) recognise SARS-CoV-2 as a pathogen
- The innate immune system can generate an appropriate immune response in mild patients, with higher inflammation (especially pro-inflammatory cytokines) in severe patients.
- In mild patients, the innate immune response is early, particularly with respect to release of type 1 and type 3 interferons. Severe patients have initially suppressed innate immune responses with later hyperactivity and may have autoantibodies to type 1 interferon.
- Pre-existing inflammatory conditions predispose to a stronger inflammatory response.
- In mild patients, there is smooth innate-to-adaptive switching, with an early and robust synchronised T and B cell response, even in the absence of serum antibodies. Mild patients have higher serum B cells and T cells but lower serum antibodies; severe patients have the reverse of this.
- Mild patients have a lower neutrophil to lymphocyte ratio (NLR). A high NLR was the most accurate predictor of progression to severe COVID.
- Children and adolescents have lower COVID infection rates, lower viral loads and lower incidence of severe COVID compared to adults. There was no evidence of excess mortality in children; treatment delays caused more children's deaths than COVID.

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