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Why should we be worried?

<table>
<thead>
<tr>
<th>Disease</th>
<th>MERS</th>
<th>SARS</th>
<th>COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed cases</td>
<td>2494</td>
<td>8096</td>
<td>7,930,989</td>
</tr>
<tr>
<td>Deaths</td>
<td>858</td>
<td>774</td>
<td>433,783</td>
</tr>
<tr>
<td>Case fatality rate</td>
<td>37%</td>
<td>9.2%</td>
<td>5.5%</td>
</tr>
</tbody>
</table>
The CIRCO approach

**Immunologists:**
Elizabeth Mann, Madhvi Menon, Joanne Konkel, John Grainger, Sean Knight, Christopher Jagger, Tovah Shaw, Siddharth Krishnan, Halima Ali Shuwa, Nicholas A. Scott, Alistair Chenery, Mehwish Younas, Kathryn Gray, Saba Khan, Emma Connelly, Miriam Franklin, Silvia Liu, Christine Chew, Flora A. McClure, Barbora Salcman, Oliver Brand, David Morgan, Ruth Stephens, Verena Kaestele, Thomas Williams, Graham Lord, Tracy Hussell

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**University Hospital of South Manchester**

**Bioinformaticians:**
Magnus.Rattray, Mike Phuychareon, Mudassar Iqbal, Syed Murtuza Baker

**NIHR Respiratory TRC/BRC:**
Alex Horsley - Manchester BRC
Tim Harrison - Nottingham BRC
Joanna Porter - UCL BRC
Ratko Djukanovic - Southampton BRC
Stefan Marciniak - Cambridge BRC
Chris Brightling - Leicester BRC
Ling-Pei Ho - Oxford BRC
Lorcan McGarvey - Queen's University Belfast
Jane Davies - Imperial College BRC

Real-time immunological analysis
Global alterations to innate and adaptive immune cells visualised by UMAP in fresh whole blood samples

17-parameter Flow cytometry
Markers associated with distinct immune populations and activation

CD16^{low} Granulocytes
Restoration of balance of T cells and neutrophils is associated with good outcome.
Monocytes play a critical role in respiratory infections.

Lung

Monocytes recruited from circulation: some differentiate

Infection and cytokine storms: monocytes mobilized from bone marrow

Bone marrow

Pool of haematopoietic stem cells

CCR2+ monocytes

INFECTION

Contribute to excess inflammation, tissue damage and fibrosis
Enhanced expression of cell cycle marker Ki67 in COVID-19 monocytes upon admission

- **Healthy**
- **COVID-19 (all)**
- **Mild COVID-19**
- **Moderate COVID-19**
- **Severe COVID-19**

Bone marrow

Premature release
Retain Ki67 expression

Emergency myelopoiesis?
Reduced expression of cyclo-oxygenase 2 (COX2) in COVID-19 monocytes

**NSAIDs**
- Ibuprofen

**Viruses**
- Hepatitis B

**Arachidonic acid**

**COX2**

**Prostaglandins** (pro-inflammatory)

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**Graphs**
- **COX-2 MFI (×10^3, a.u.)**
  - Healthy
  - COVID-19 (all)
  - Mild COVID-19
  - Moderate COVID-19
  - Severe COVID-19

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**Acronyms**
- COX2: Cyclo-oxygenase 2
- NSAIDs: Nonsteroidal anti-inflammatory drugs
- Viruses
- Hepatitis B
What happens to monocytes throughout the COVID-19 disease course?

Ki67 drops rapidly regardless of disease outcome: early severity predictor

COX2 increases with recovery, stays low during ITU
What happens to cytokine storm throughout the COVID-19 disease course?

Systemic cytokines drop soon after ITU admission

IL-6

IP-10

MCP-1

Inflammatory: Innate cells

Innate cell migration

Structural and physiological damage in ITU: critical window for targeting immune response early after admission
<table>
<thead>
<tr>
<th>Age</th>
<th>Median</th>
<th>95% CrI (lower)</th>
<th>95% CrI (upper)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1year,1-4</td>
<td>0.00045%</td>
<td>7.8e-05%</td>
<td>0.002%</td>
</tr>
<tr>
<td>5-14</td>
<td>0.0013%</td>
<td>0.00071%</td>
<td>0.0023%</td>
</tr>
<tr>
<td>15-24</td>
<td>0.0043%</td>
<td>0.0029%</td>
<td>0.0062%</td>
</tr>
<tr>
<td>25-44</td>
<td>0.029%</td>
<td>0.025%</td>
<td>0.034%</td>
</tr>
<tr>
<td>45-64</td>
<td>0.44%</td>
<td>0.4%</td>
<td>0.49%</td>
</tr>
<tr>
<td>65-74</td>
<td>2.9%</td>
<td>2.6%</td>
<td>3.2%</td>
</tr>
<tr>
<td>75+</td>
<td>17%</td>
<td>14%</td>
<td>22%</td>
</tr>
</tbody>
</table>

(Accessed: 14/07/2020)
## Patient details:

<table>
<thead>
<tr>
<th></th>
<th>All patients (49)</th>
<th>Mild (18)</th>
<th>Moderate (21)</th>
<th>Severe (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>61 (51 – 71)</td>
<td>61.5 (45 – 72.5)</td>
<td>59 (51 – 68)</td>
<td>66 (52 – 72.5)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31 (63.3%)</td>
<td>11 (61.1%)</td>
<td>13 (62%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Female</td>
<td>18 (36.7%)</td>
<td>7 (38.9%)</td>
<td>8 (38%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>27.5 (24.9 - 30)</td>
<td>27.1 (23.6 - 30)</td>
<td>28.3 (25.7 - 30)</td>
<td>26.5 (24.9 - 30.4)</td>
</tr>
<tr>
<td><strong>Co-morbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>8/49 (16.3%)</td>
<td>3/18 (16.7%)</td>
<td>2/21 (9.5%)</td>
<td>3/10 (30%)</td>
</tr>
<tr>
<td>IHD</td>
<td>5/49 (10.2%)</td>
<td>2/18 (11.1%)</td>
<td>1/21 (4.8%)</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>HTN</td>
<td>14/49 (28.6%)</td>
<td>5/18 (27.8%)</td>
<td>7/21 (33.3%)</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>COPD</td>
<td>9/49 (18.4%)</td>
<td>4/18 (22.2%)</td>
<td>4/21 (19.1%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>5/49 (10.2%)</td>
<td>2/18 (11.1%)</td>
<td>3/21 (14.3%)</td>
<td>0/10 (0%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3/49 (6.1%)</td>
<td>0/18 (0%)</td>
<td>1/21 (4.8%)</td>
<td>2/10, (20%)</td>
</tr>
</tbody>
</table>
So what? Our results have clinical implications:

Disease severity is driven by the innate immune system

Patients who go on to have severe COVID-19 can be identified on admission: High Ki-67, Low COX-2, Low T cells, High neutrophils

The cytokine storm abates prior to ITU
Use of non-steroidal anti-inflammatory drugs (NSAIDs) would compound the already low COX-2

Recommended therapeutics:
To stop recruitment of immune cells: complement anaphylatoxin C5a or IL-8 (CXCL8)

To stop bone marrow release: Inhibit CXCR2

To stop neutrophil survival: Neutrophil elastase inhibitors and inhibition of G-CSF, IL-23

To reduce neutrophil effects: Target toxic products such as S100A1/A2, HMGB1 and free radicals, formation of NETS
The One Manchester approach

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