Intestinal adverse outcomes in COVID-19: current evidence and uncertainties using the Adverse Outcome Pathway framework.

Laure-Alix Clerbaux[1]*, Julija Fillipovska[2], Amalia Muñoz[3], Mauro Petrillo[4], Helena Soares[5], Sally Mayasich[6], Maria-Joao Amorim[7], Lucia Grenga[8].

[1.]European Commission, Joint Research Centre (JRC), Ispra, Italy; [2.]Independent scientist, Ohrid, North Macedonia; [3.]European Commission, Joint Research Centre (JRC), Geel, Belgium; [4.]Seidor Italy srl, Milano, Italy; [5.]Human Immunobiology and Pathogenesis Group, CEDOC, NOVA Medical School | Faculdade de Ciências Médicas, NOVA University of Lisbon, Lisbon, Portugal;[6.]University of Wisconsin-Madison Aquatic Sciences Center at US EPA, Duluth, MN, USA;[7.]Instituto Gulbenkian de Ciência, Lisbon, Portugal;[8.]Université Paris-Saclay, CEA, INRAE, Département Médicaments et Technologies pour la Santé, Paris, France;
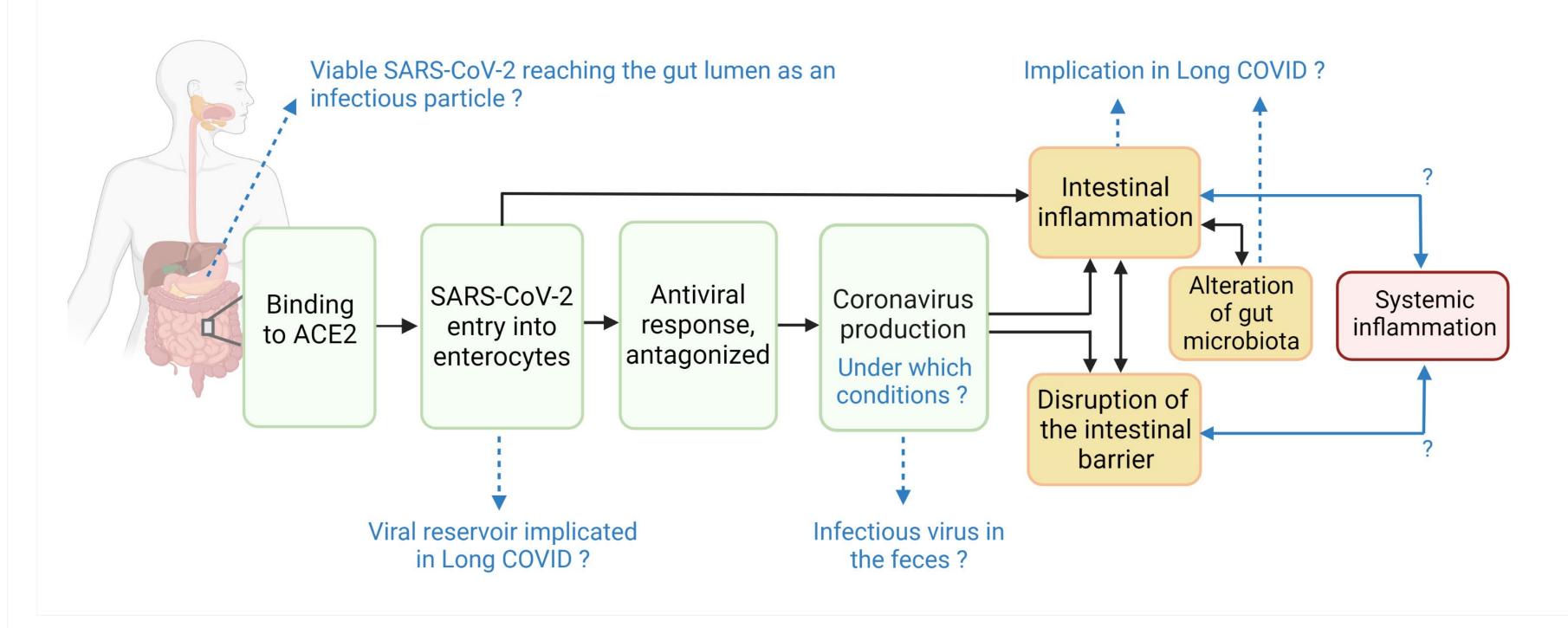*contact: Laure-Alix.Clerbaux@ec.europa.eu

Background and objectives.

COVID-19 patients could experience gastrointestinal disorders and alteration of gut microbiota. Besides, the SARS-CoV-2 receptor ACE2 is highly expressed in enterocytes. Thus, it has been proposed that SARS-CoV-2 enteric infection leads to intestinal barrier disruption, inflammation, and dysbiosis. However, the underlying mechanisms are still poorly understood.

Methods.

Within the **CIAO project**, we applied the Adverse Outcome Pathway (AOP) framework to explore existing evidence supporting the sequence of events of proposed pathways behind SARS-CoV-2 mediated gut pathophysiology.
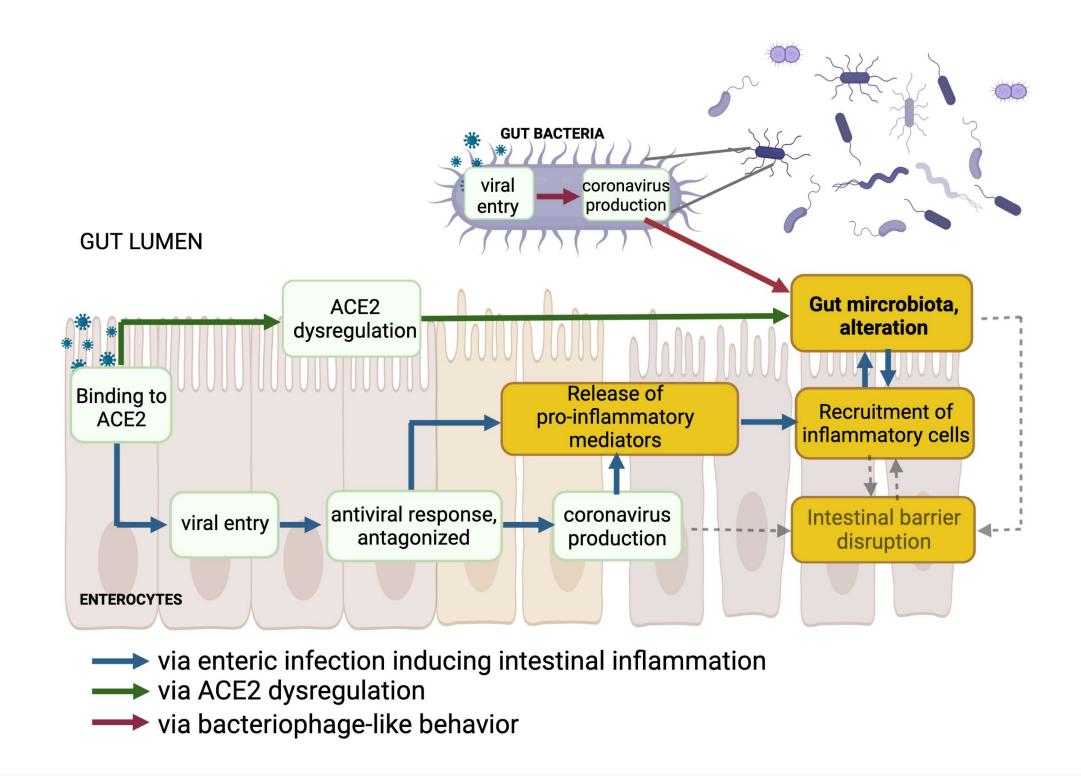
Results.

One AOP outlines SARS-CoV-2 enteric infection leading to intestinal barrier dysfunction via cytopathic effects. Studies with human enterocytes *in vitro* demonstrate SARS-CoV-2 infection. However, evidence for the viral replication *in vivo* in animals and in (healthy) human gut is unclear, either due to timely interferon response limiting viral replication or the multiple layered barrier. While the biological plausibility is high, currently, there is not enough evidence to support enterocyte massive cell death due to SARS-CoV-2 infection.

Besides, ACE2 plays a key role in intestinal homeostasis, notably in dietary amino acids uptake, such as tryptophan. Evidence supports high plausibility for intestinal ACE2 dysregulation due to spike (S) protein binding, but further examination is needed to distinguish between the direct effect of the spike protein ACE2 binding and subsequent replication. In addition, more evidence is required to understand the role of observed tryptophan alteration which regulates the secretion of antimicrobial peptides, altering the gut microbiota. Lastly, another putative AOP proposes a new mechanism for COVID-19 transmission mediated by gut bacteria that may be transducing infective SARS-CoV-2 components. Current inconsistencies regarding detection of replicating SARS-CoV-2 in feces calls for additional research.

Conclusion.

This AOP-aligned approach highlights current knowledge gaps and inconsistencies in the evidence that can guide future research. In addition, AOP facilitates synergy from different disciplines to address this health issue of societal importance.

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