

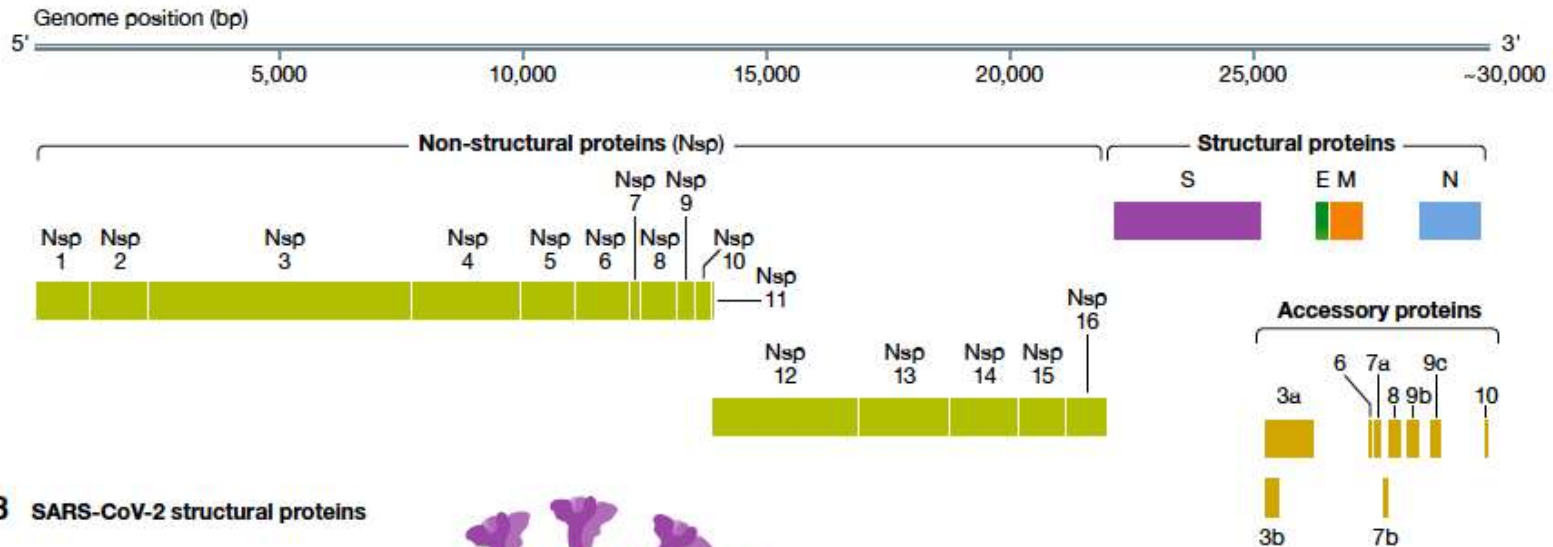
*Lecture immunologiche, da Tucidide a Camus: <https://www.repubblica.it/salute/dossier/noi-e-loro/>*

**Fondazione Humanitas per la Ricerca e Piccolo Teatro di Milano:** Daniela Minerva, Claudio Longhi; lette da Sonia Bergamasco e Neri Marcoré, commento di Alberto Mantovani

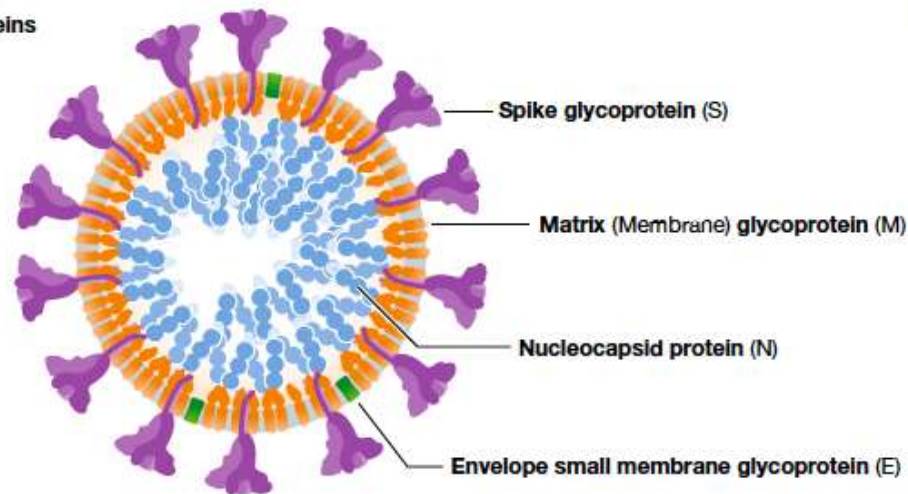
*(Tucidides, The Peloponnesian wars, Book 2, The Plague in Athens)*

# SARS-CoV-2 genome and proteins

## A SARS-CoV-2 genome



## B SARS-CoV-2 structural proteins

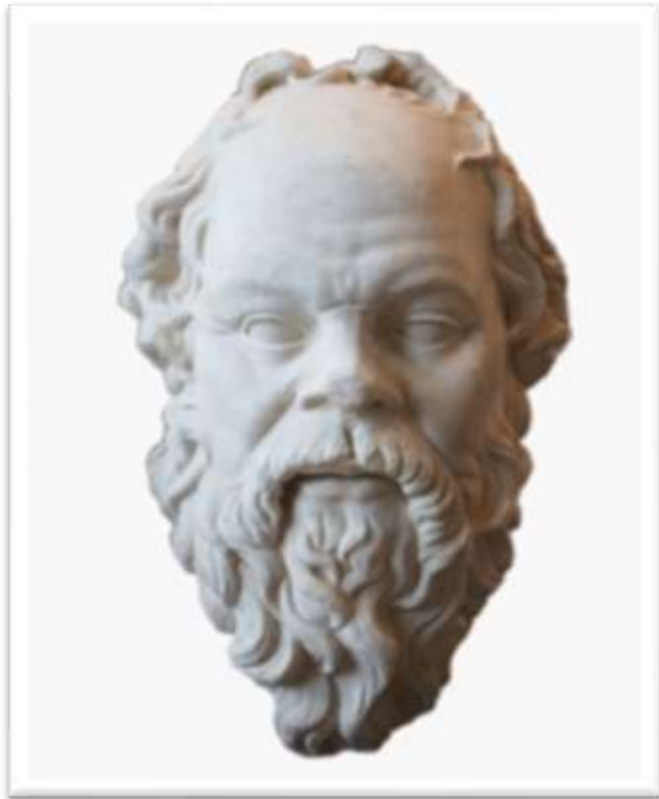


(SARS-CoV-2 as seen by three of my grandchildren Tommaso, Mattia and Agata)

# «Έτσι, δεν γνωρίζω»

*«I know I do not know»*

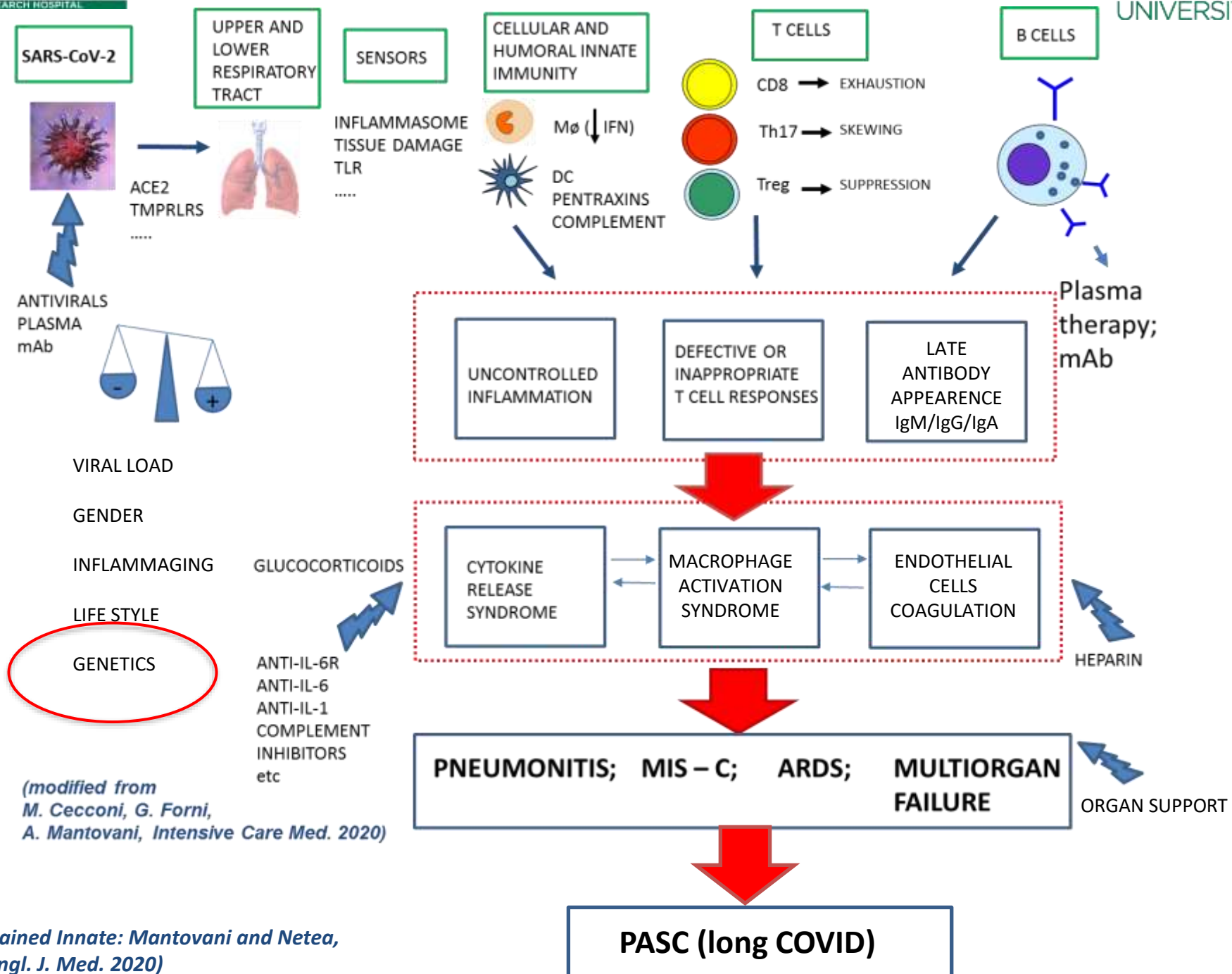
**(Socrates)**



[https://www.lincai.it/sites/default/files/documenti/Commissioni/Health\\_committee\\_Covid19\\_Summer\\_report\\_July2020.pdf](https://www.lincai.it/sites/default/files/documenti/Commissioni/Health_committee_Covid19_Summer_report_July2020.pdf)

<https://www.lincai.it/it/article/covid-19-vaccines-november-2020-report>

*M. Cecconi, G. Forni, A. and Mantovani, Intensive Care Medicine 2020*



# Host genetics and COVID-19

www.aging-us.com

AGING 2020, Vol. 12, No. 11

Research Paper

## *ACE2* and *TMPRSS2* variants and expression as candidates to sex and country differences in COVID-19 severity in Italy

Rosanna Asselta<sup>1,2,\*</sup>, Elvezia Maria Paraboschi<sup>1,2,\*</sup>, Alberto Mantovani<sup>1,2,3</sup>, Stefano Duga<sup>1,2</sup>

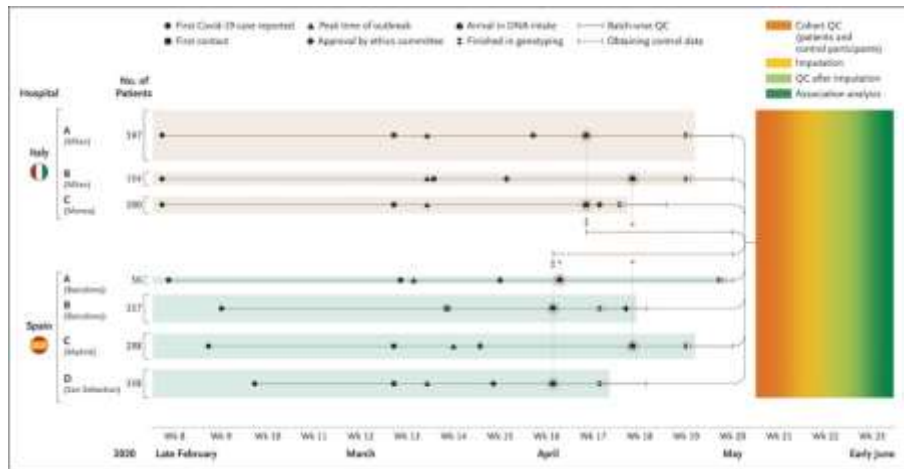
THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

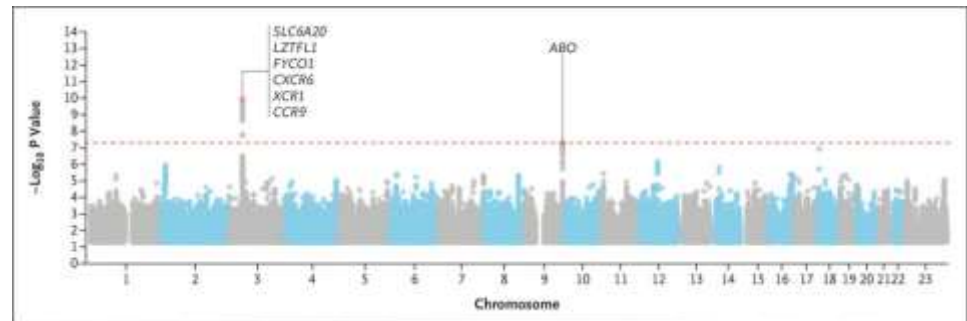
## Genomewide Association Study of Severe Covid-19 with Respiratory Failure

The Severe Covid-19 GWAS Group\*

## Timeline of rapid COVID-19 GWAS



Manhattan Plot of the meta-analysis highlighting the two susceptibility loci for Severe COVID-19 with Respiratory Failure



Ellinghaus D, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *N Engl J Med*. 2020;NEJMoa2020283.



## TITLE

Mapping the human genetic architecture of COVID-19 by worldwide meta-analysis

## AUTHORS

The COVID-19 Host Genetics Initiative

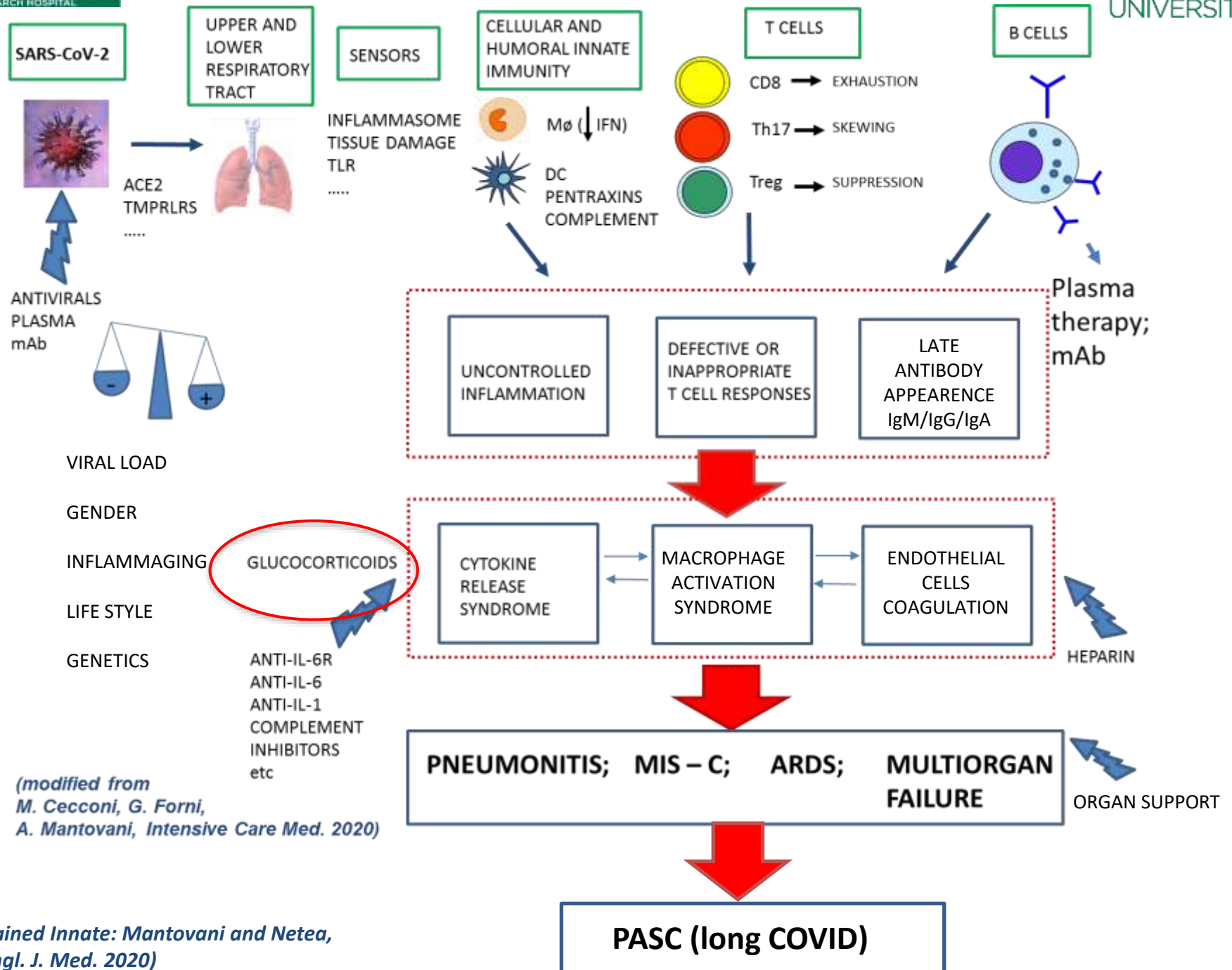
[The complete list of authors can be found online at: [COVID19-HGI authorship list](#) ]

*Address for correspondence:*

Dr Andrea Ganna, Institute for Molecular Medicine Finland, Tukholmankatu 8, Helsinki  
email: [andrea.ganna@helsinki.fi](mailto:andrea.ganna@helsinki.fi)

## ABSTRACT

The genetic makeup of an individual contributes to susceptibility and response to viral infection. While environmental, clinical and social factors play a role in exposure to SARS-CoV-2 and COVID-19 disease severity, host genetics may also be important. Identifying host-specific genetic factors indicate biological mechanisms of therapeutic relevance and clarify causal relationships of modifiable environmental risk factors for SARS-CoV-2 infection and outcomes. We formed a global network of researchers to investigate the role of human genetics in SARS-COV-2 infection and COVID-19 severity. We describe the results of three genome-wide association meta-analyses comprising 49,562 COVID-19 patients from 46 studies across 19 countries worldwide. We reported 15 genome-wide significant loci that are associated with SARS-CoV-2 infection or severe manifestations of COVID-19. Several of these loci correspond to previously documented associations to lung or autoimmune and inflammatory diseases. They also represent potentially actionable mechanisms in response to infection. We further identified smoking and body mass index as causal risk factors for severe COVID-19. The identification of novel host genetic factors associated with COVID-19, with unprecedented speed, was enabled by prioritization of shared resources and analytical frameworks. This working model of international collaboration a blue-print for future genetic discoveries in the event of pandemics or for any complex human disease.





## RAPID RECOMMENDATIONS

### A living WHO guideline on drugs for covid-19

Reed Siemieniuk,<sup>1,2,a</sup> Bram Rochwerf,<sup>1,2,a</sup> Thomas Agoritsas,<sup>1,3,4,b</sup> François Lamontagne,<sup>5,b</sup> Yee-Sin Leo,<sup>6,a,b</sup> Helen Macdonald,<sup>7</sup> Arnab Agarwal,<sup>8</sup> Linan Zeng,<sup>1</sup> Lyubov Lytvyn,<sup>1</sup> John Adabie Appiah,<sup>9,b</sup> Wagdy Amin,<sup>10,a</sup> Yaseen Arabi,<sup>11,b</sup> Lucille Blumberg,<sup>12,b</sup> Erlina Burhan,<sup>13,a</sup> Frederique Jacqueroz Bausch,<sup>14,a</sup> Carolyn S Calfee,<sup>15,b</sup> Bin Cao,<sup>16,b</sup> Maurizio Cecconi,<sup>17,a,b</sup> Duncan Chanda,<sup>18,a</sup> Graham Cooke,<sup>19,b</sup> Bin Du,<sup>20,a</sup> Jake Dunning,<sup>21,b</sup> Heike Geduld,<sup>22,a,b</sup> Patrick Gee,<sup>23,a,b</sup> Madiha Hashimi,<sup>24,a</sup> David S Hui,<sup>25,b</sup> Sushil Kabra,<sup>26,a</sup> Seema Kanda,<sup>27,a,b</sup> Leticia Kawano-Dourado,<sup>28,a,b</sup> Yae-Jean Kim,<sup>29,a,b</sup> Niranjana Kissoon,<sup>30,a,b</sup> Arthur Kwizera,<sup>31,a,b</sup> Jon Henrik Laake,<sup>32,b</sup> Flavia R Machado,<sup>33,b</sup> Imelda Mahaka,<sup>34,a</sup> Hela Manai,<sup>35,a</sup> Greta Mino,<sup>36,a</sup> Emmanuel Nsutebu,<sup>37,a</sup> Natalia Pshenichnaya,<sup>38,a</sup> Nida Qadir,<sup>39,a,b</sup> Saniya Sabzwari,<sup>40,b</sup> Rohit Sarin,<sup>41,a,b</sup> Michael Sharland,<sup>42,a</sup> Yinzong Shen,<sup>43,a,b</sup> Shalini Sri Ranganathan,<sup>44,a</sup> Joao Souza,<sup>45,a</sup> Sebastian Ugarte,<sup>46,a</sup> Sridhar Venkatapuram,<sup>47,a</sup> Vu Quoc Dat,<sup>48,a</sup> Dubula Vuyiseka,<sup>49,a</sup> Miriam Stegemann,<sup>50</sup> Ananda Wijewickrama,<sup>51,a</sup> Brittany Maguire,<sup>52</sup> Dena Zeraatkar,<sup>1</sup> Jessica Bartoszko,<sup>1</sup> Long Ge,<sup>1,53</sup> Romina Brignardello-Petersen,<sup>1</sup> Andrew Owen,<sup>54</sup> Gordon Guyatt,<sup>1,2</sup> Janet Diaz,<sup>55,c</sup> Michael Jacobs,<sup>56,a,c</sup> Per Olav Vandvik<sup>4,57,c</sup>

the **bmj** | *BMJ* 2020;370:m3379 | doi: 10.1136/bmj.m3379

THE NEW ENGLAND JOURNAL OF MEDICINE

## ORIGINAL ARTICLE

# Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

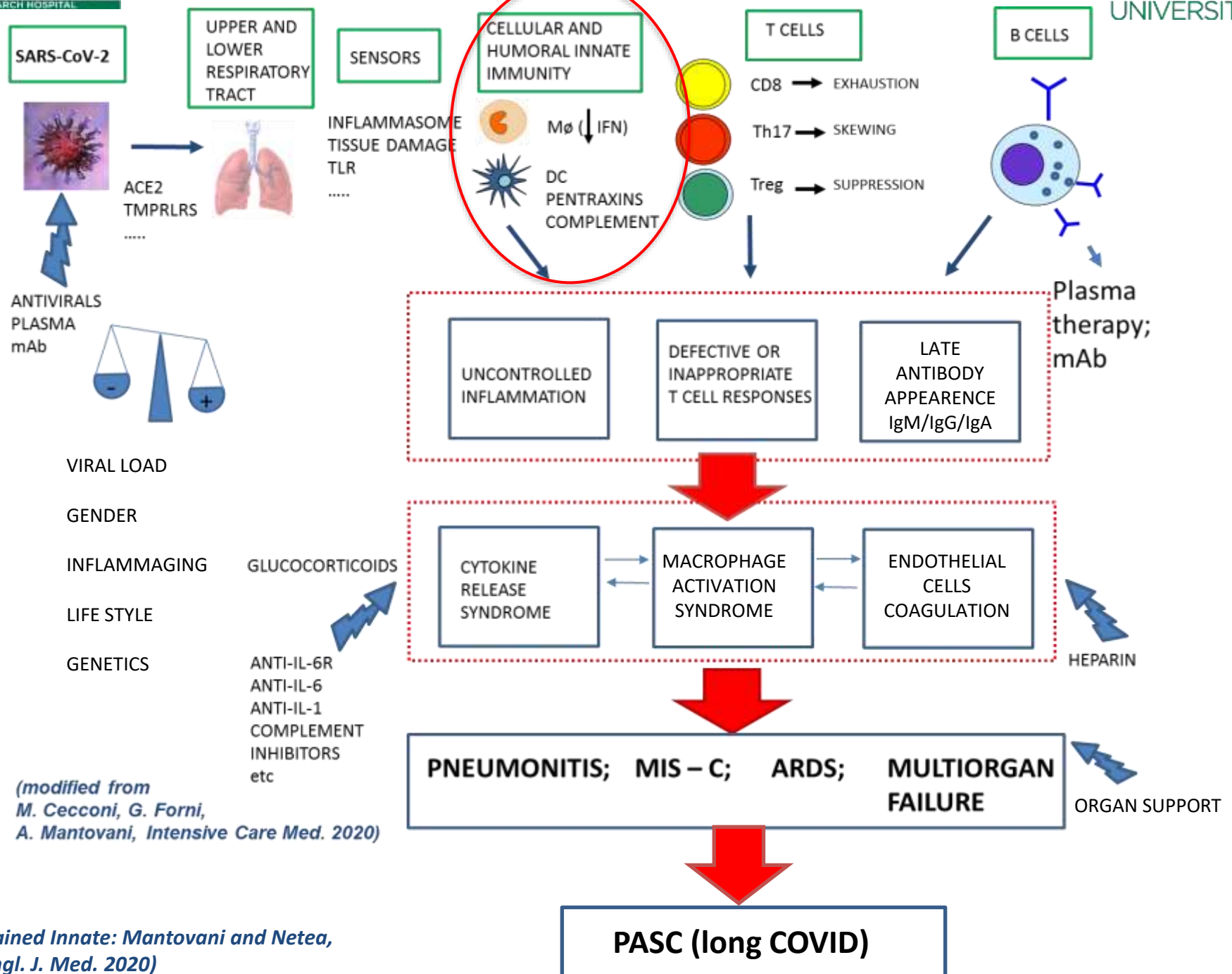
The RECOVERY Collaborative Group\*

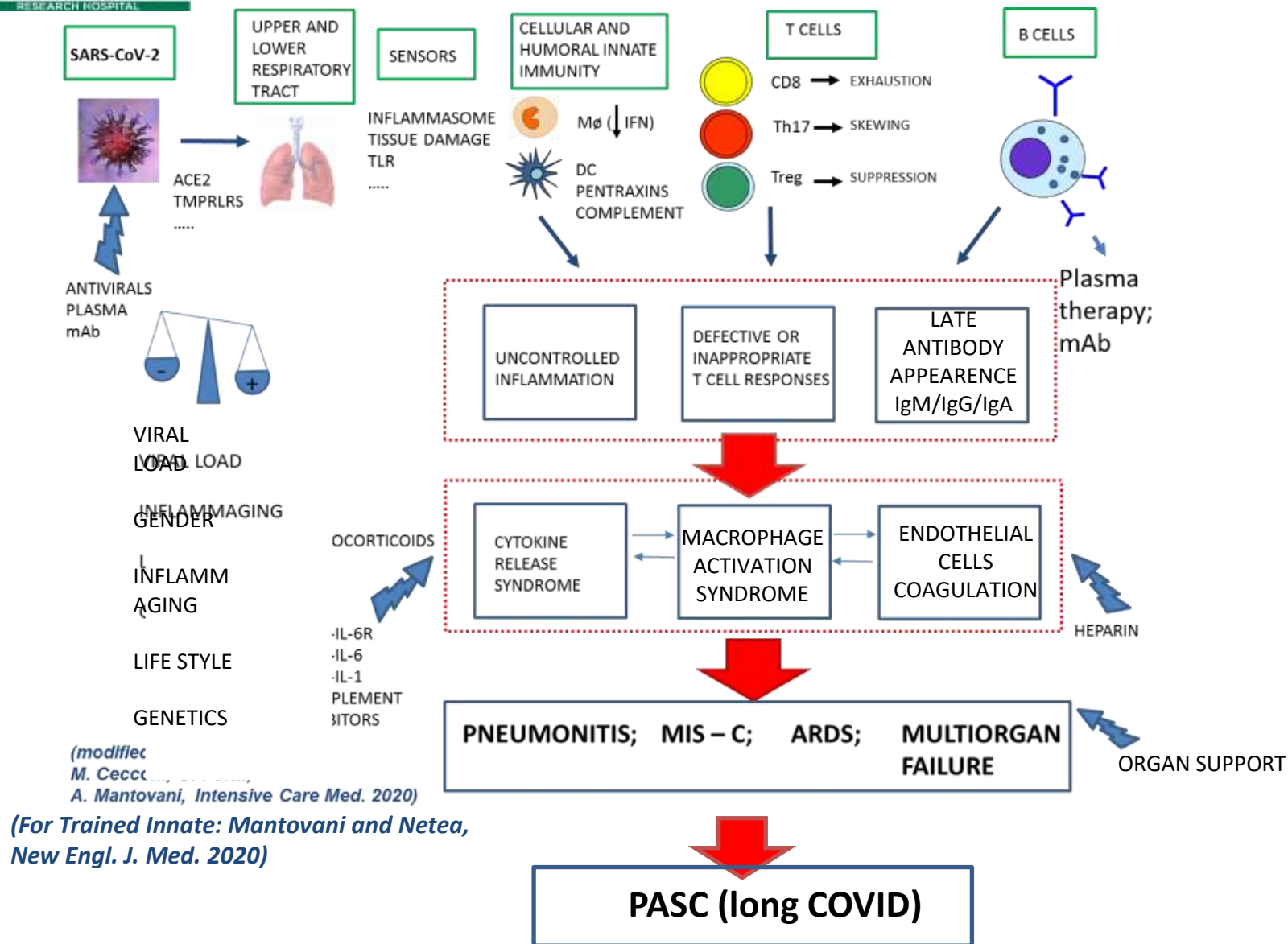
**Table 1** Clinical features of 1171 patients positive for SARS-CoV-2 admitted to the Humanitas Hospital Emergency Department between September 15 and December 15 in 2020 arrayed according the outcome of the evaluation (discharged/admitted) and the prior use of oral glucocorticoids (OGC)

	Discharged		Admitted	
	Without OGC (n=358)	With OGC (n=27)	Without OGC (n=264)	With OGC (n=522)
Age (years)	55.0 (19.0)	55.4 (19.3)	72.2 (15.1)	71.2 (13.9)
Female sex (n)	168 (47%)	13 (48%)	111 (42%)	192 (37%)
Death (n)	28 (7.8%)	1 (3.7%)	48 (18.2%)	105 (20.1%)
Respiratory rate (/min)	18.0 (2.4)	17.7 (1.2)	18.5 (4.8)	18.9 (2.4)
Heart rate (/min)	85.8 (15.9)	84.0 (11.1)	85.1 (15.1)	82.7 (14.4)
Glasgow Coma Scale	14.6 (1.6)	14.9 (0.2)	14.9 (0.6)	14.9 (0.8)
O <sub>2</sub> saturation (%)	99.0 (4.8)	96.3 (4.0)	95.4 (5.2)	91.3 (5.6)
Systolic pressure (mm Hg)	126.8 (21.2)	123.5 (12.5)	128.2 (20.6)	127.0 (16.0)
Diastolic pressure (mm Hg)	79.6 (7.4)	74.9 (6.8)	72.7 (14.0)	74.1 (11.3)
Body temperature (°C)	36.7 (0.7)	36.8 (0.4)	37.7 (16.9)	37.1 (3.4)

Variables are expressed as number (%) or mean (SD).

*(De Santis et al., Ann Rheum Dis., 2021)*





**COVID-19: AT THE INTERCEPTION OF GENETIC PREDISPOSITION, GENETIC IMMUNODEFICIENCY UNMASKED BY THE VIRUS, AUTOIMMUNITY AND UNCONTROLLED INFLAMMATION**

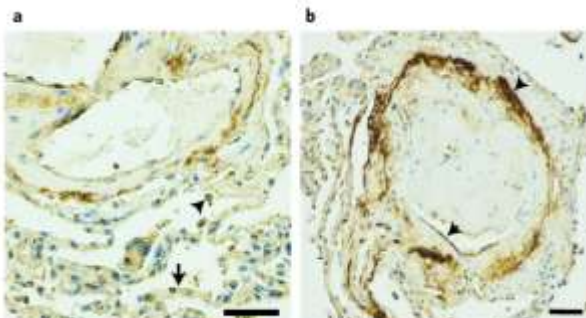
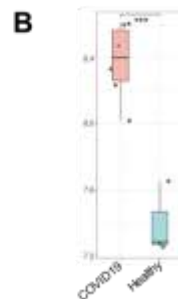
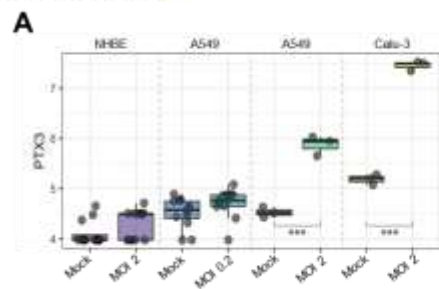
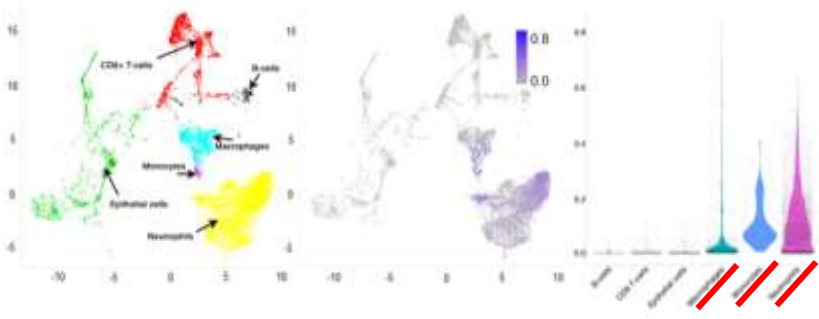
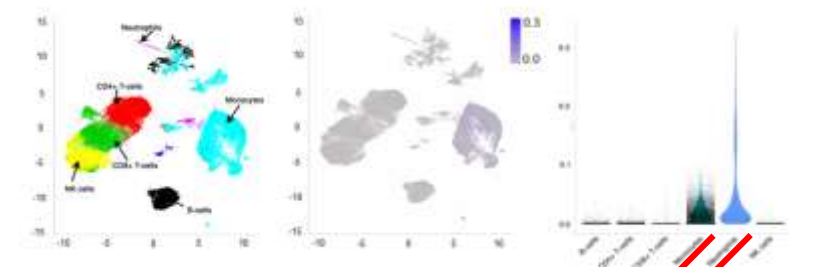


# Macrophage expression and prognostic significance of the long pentraxin PTX3 in COVID-19

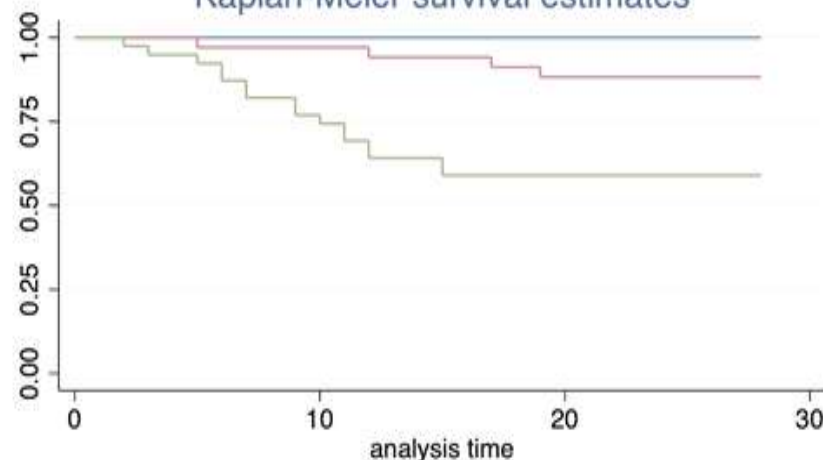
Enrico Brunetta<sup>1,2,10</sup>, Marco Folci<sup>1,2,10</sup>, Barbara Bottazzi<sup>1,30</sup>, Maria De Santis<sup>1</sup>, Giuseppe Gritti<sup>3</sup>, Alessandro Protti<sup>1,2</sup>, Sarah N. Mapelli<sup>1</sup>, Stefanos Bonovas<sup>1,2</sup>, Daniele Piovani<sup>1,2</sup>, Roberto Leone<sup>1</sup>, Ilaria My<sup>1,2</sup>, Veronica Zanon<sup>1</sup>, Gianmarco Spata<sup>1</sup>, Monica Bacci<sup>1</sup>, Domenico Supino<sup>2</sup>, Silvia Carnevale<sup>2</sup>, Marina Sironi<sup>1</sup>, Sadaf Davoudian<sup>1</sup>, Clelia Peano<sup>1,4</sup>, Francesco Landi<sup>3</sup>, Fabiano Di Marco<sup>5,6</sup>, Federico Raimondi<sup>5</sup>, Andrea Gianatti<sup>7</sup>, Claudio Angelini<sup>1</sup>, Alessandro Rambaldi<sup>3,8,9</sup>, Cecilia Garlanda<sup>1,2,9</sup>, Michele Ciccarelli<sup>1</sup>, Maurizio Cecconi<sup>1,2,9</sup> and Alberto Mantovani<sup>1,2,9</sup>

PBMC

BAL



Kaplan-Meier survival estimates



# **LADY MONTAGUE and COTTON MOTHER: 1721-2021, 300 YEAR ANNIVERSITY THE FIRST INOCULATION/VACCINATION CLINICAL TRIAL AND REAL WORLD ASSESSMENT**



**Princess Caroline requested to Sir Hans Sloane her children be inoculated. He refused to perform the procedure himself**

**George I, her father-in-law, gave permission for girls, not boys**

**She coaxed him into setting up Newgate Prison experiment 1721**

**Medical, political, media witnesses**

**Maitland performed inoculations**

**6 prisoners offered pardon in exchange for inoculation**

**1 had already had smallpox-used as a control**

**After recovery, 1 subject was sent to sleep in the same bed as a smallpox infected child- test of efficacy.**

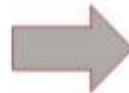
*(inspired by Professor B. M. Assael and modified from his slides)*



# COVID-19 vaccines: Where we stand and challenges ahead.

Twelve candidate vaccines currently in Phase III trial.  
COVID-19 vaccines based on the whole inactivated SARS-CoV-2.

**Virus SARS-CoV-2**



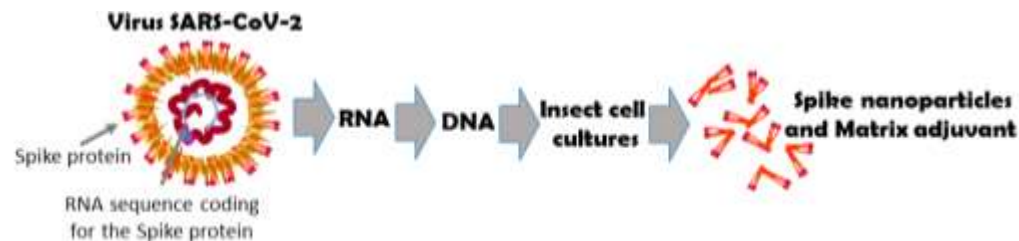
**Vaccines based on inactivated whole SARS-CoV-2 virus**

Company and country	Vaccine name	Number of doses	Approval and registration
Sinovac Biotech, China	---	2	Ahead of Phase II trial it is offered to essential workers and other high high risk people of the Chinese town of Jiaxing for about 30 €/dose
Beijing Institute of Biological Products and Sinopharm, China	BBIBP-CorV	2	Limited approval for Chinese health care workers and soldiers ahead of Phase III trial
Wuhan Institute of Biological Products, China	---	2	Limited approval for Chinese health care workers and soldiers ahead of Phase III trial
Bharat Biotech, India	COVAXIN	2	The Phase III trial with 26 000 volunteers is expected to close in February 2021.

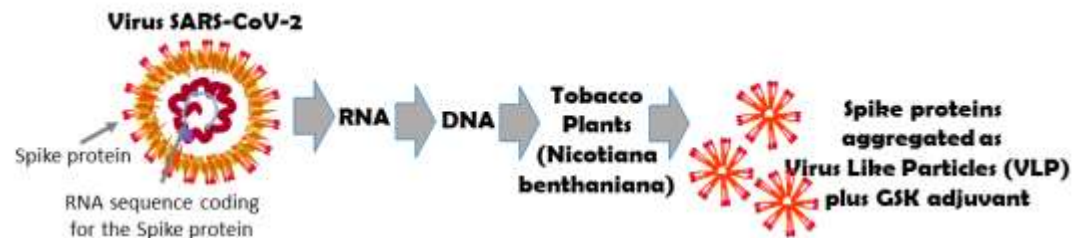
# COVID-19 vaccines: Where we stand and challenges ahead

Twelve candidate vaccines currently in Phase III trial:

**COVID-19 Vaccines based on Spike protein.**



Company and country	Vaccine name	Number of doses	Approval and registration
Novavax, US	NVX-CoV2373	2	A first Phase III trial of 15,000 volunteers was launched in the UK. A second Phase III is enrolling 30 000 volunteers in the US and Mexico.

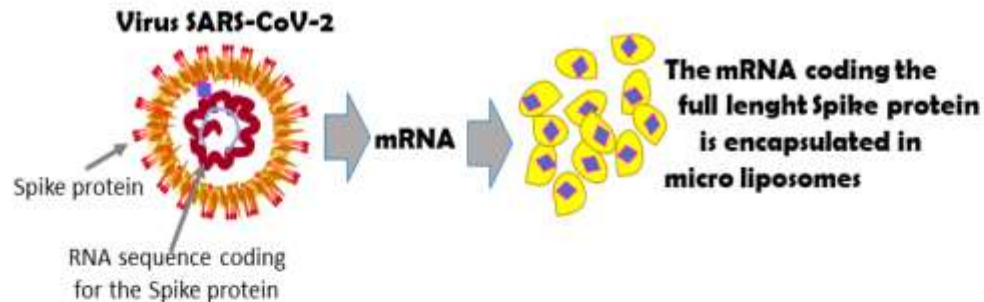


Company and country	Vaccine name	Number of doses	Approval and registration
Medicago, Canada and GSK, Italy	Co-VLP	2	A Phase III trial is enrolling in over 30 000 subjects in North America, Latin America and Europe

# COVID-19 vaccines: Where we stand and challenges ahead

Twelve candidate vaccines currently in Phase III trial:

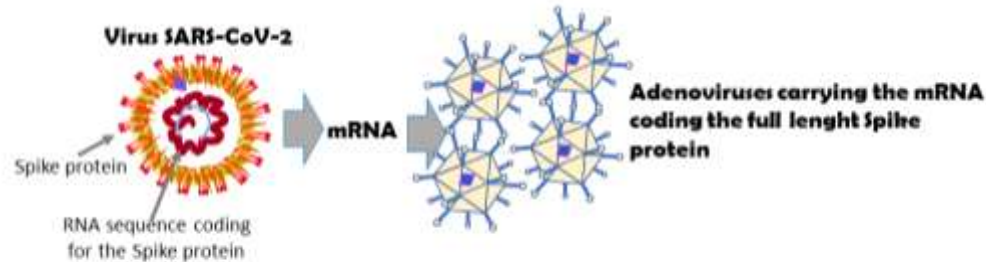
**COVID-19 Vaccines based on Spike protein mRNA carried by lipidic microparticles.**



Company and country	Vaccine name	Number of doses	Approval and registration
Pfizer, USA and BioNTech, Germany	BNT162b2	2	Final results of the Phase III trial enrolling 45 539 participants demonstrated BNT162b2 vaccine to be 95% effective. Pfizer started vaccine registration process at UK, US, Brasil and EU regulatory agencies.
Moderna USA and US Governement	mRNA-1273	2	Final results of the Phase III trial in the US enrolling 30 000 people showed 94% vaccine efficacy and nobody who was vaccinated with mRNA-1273 developed severe COVID-19. A rolling review of trial data by US, UK and EU regulatory agencies is ongoing.

# COVID-19 vaccines: Where we stand and challenges ahead

## COVID-19 Vaccines based on Spike protein encoded by adenoviruses



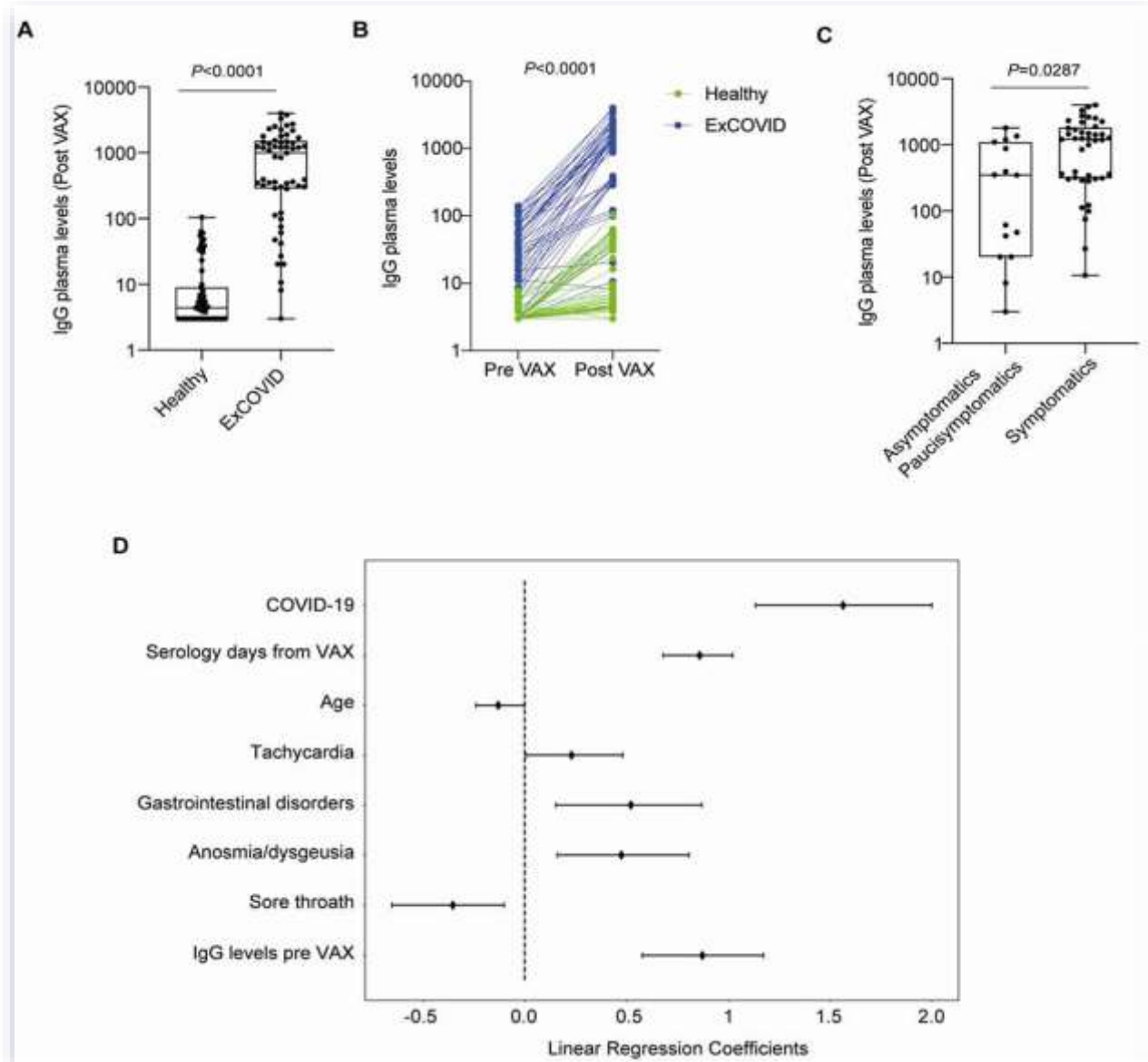
Company and country	Vaccine name	Number of doses	Approval and registration
CanSino Biologicals	Ad5-nCoV	1	This vaccine is based on the human adenovirus Ad5 carrying the mRNA for the Spike protein is approved for administration to Chinese health care workers and soldiers ahead of the end of Phase III trial.
Gamaleya Res Inst, Russia	Sputnik V	2	This vaccine based on two human adenoviruses (Ad5 and Ad26) carrying the mRNA for the Spike protein administered sequentially was approved for limited use ahead of the end of Phase III trial.
Johnson&Johnson, USA	Ad26COVs1	1	The Phase III trial based on a human adenovirus Ad26 carrying the mRNA for the Spike protein with up to 60 000 participants is expected to finish by the end of 2020. A second Phase III trial was launched to observe the effects of two doses of the vaccine.
AstraZeneca, Sweden- UK Univ. Oxford, UK	ChAdOx1	2	The Phase III trial on this vaccine is based on a chimpanzee adenovirus carrying the mRNA for the Spike protein led only to 62 percent efficacy. However, when ChAdOx1 was given first half dose, followed by a full dose, the protection climbed to 90%. Additional studies are underway to determine the efficacy of this vaccine.





*Ligabue*

# Ex COVID subjects increase exponentially anti-Spike 1/2 IgG levels after the first jab



(Levi, Azzolini, Pozzi et al, MedRxiv, 2021; J Clin Invest in press)



**National Project on Vaccines, COVID and frail patients.  
A multicentric observational prospective study to assess the  
immune response of COVID-19 vaccination in frail patients.**

**EudraCT Number:**

**ID CODE:** VAX4FRAIL study

**Version 1;** date 17 March 2021

**Sponsor:** AUSL-IRCCS Reggio Emilia

**Study Type:** Multicentric, observational

**Principal Investigator** (alphabetical order):

Dott. Giovanni Apolone (INT Milano),

Dott. Massimo Costantini (AUSL-IRCCS Reggio Emilia),

Prof. Alberto Mantovani (IRCCS Humanitas, Milano),

**Steering Committee** (alphabetic order):

Dott. Giovanni Apolone (INT Milano),

Prof. Fabio Ciceri (IRCCS San Raffaele, Milano)

Prof. Gennaro Ciliberto (IRCCS Regina Elena-IFO, Roma)

Dott. Massimo Costantini (AUSL-IRCCS Reggio Emilia),

Prof. Giuseppe Ippolito (IRCCS Spallanzani, Roma)

Prof. Franco Locatelli (Università La Sapienza, Roma)

Prof. Alberto Mantovani (IRCCS Humanitas, Milano),

Prof. Fausto Baldanti (IRCCS Policlinico San Matteo, Pavia)

Prof. Aldo Morrone (IRCCS San Gallicano-IFO, Roma)

Prof. Nicola Silvestris (IRCCS Oncologico, Bari)

Prof. Fabrizio Tagliavini (IRCCS Besta, Milano),

Prof. Antonio Uccelli (IRCCS Policlinico San Martino, Genova)

Prof. Pier Luigi Zinzani (IRCCS Sant'Orsola, Bologna)

**Disease groups referents**

1. HAEMATOLOGICAL MALIGNANCIES

Dott. Paolo Corradini, IRCCS INT Milano

2. SOLID TUMORS

Prof. Gennaro Ciliberto, IRCCS Regina Elena-IFO, Roma

3. IMMUNORHEUMATOLOGICAL DISEASES

Prof. Carlo Salvarani, AUSL-IRCCS Reggio Emilia

4. NEUROLOGICAL DISEASES

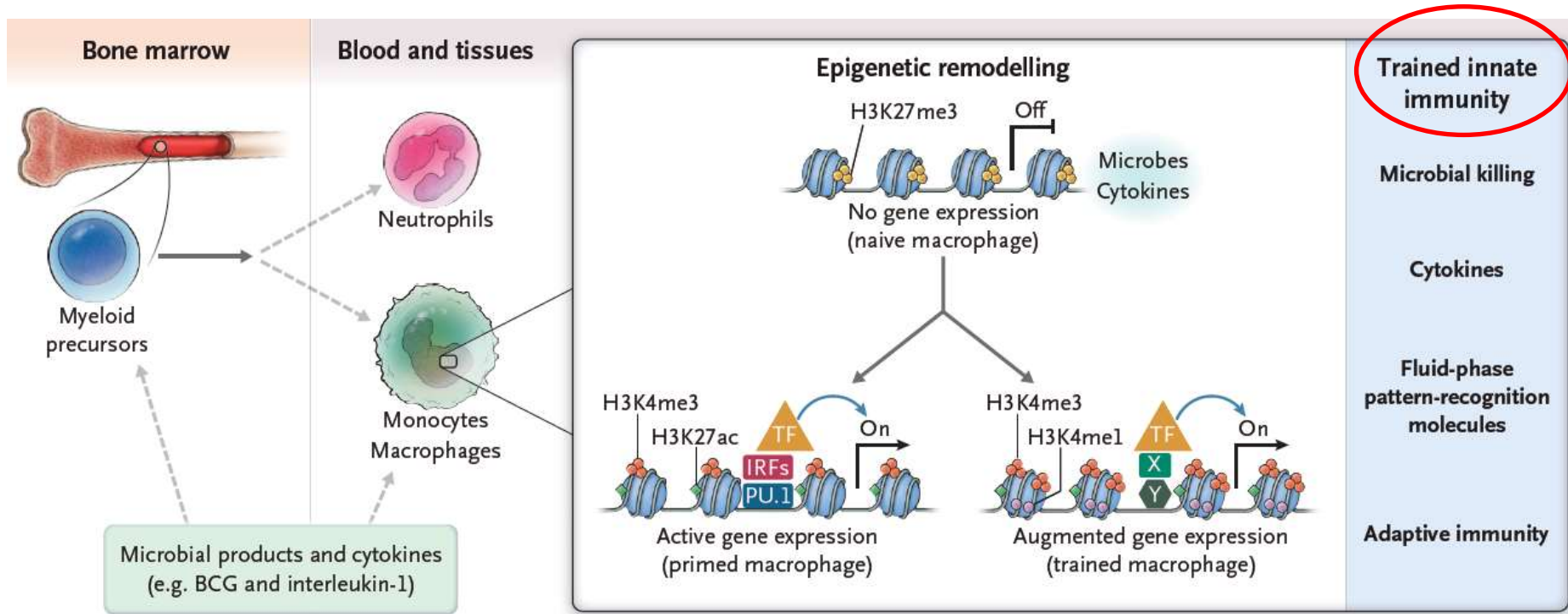
Prof. Antonio Uccelli, IRCCS Policlinico San Martino, Genova

**Immunological referents**

Dott.ssa Chiara Agrati, IRCCS Spallanzani, Roma

Prof.ssa Maria Rescigno, IRCCS Humanitas, Milano,

# Cellular and Molecular Mechanisms Underlying Trained Innate Immunity in Response to Vaccines, Microbial Products and Cytokines



(Mantovani, Netea. Trained Innate Immunity, Epigenetics, and Covid-19, New England Journal of Medicine, 2020 )

# REASONS FOR HOPE: COVAX

## 2000- 2010: GAVI's 10TH ANNIVERSARY

Clemens J, Holmgren J, Kaufmann SHE, Mantovani A:  
**Ten years of the Global Alliance for Vaccines and Immunization:  
challenges and progress** *Nature Immunology* 2010 .



Published Online: 3 December, 2018 | Supp Info: <http://doi.org/10.1084/jem.20182160>  
Downloaded from [jem.rupress.org](http://jem.rupress.org) on January 30, 2019



## VIEWPOINT

# Vaccines: An achievement of civilization, a human right, our health insurance for the future

Rino Rappuoli<sup>1,2</sup>, Angela Santoni<sup>3</sup>, and Alberto Mantovani<sup>4,5,6</sup> 

Vaccines have made a key, cost-effective contribution to the prolongation of life expectancy and quality. Here we summarize challenges facing vaccinology and immunology at the level of society, scientific innovation, and technology in a global health perspective. We argue that vaccines represent a safety belt and life insurance for humankind.



# Noi e loro

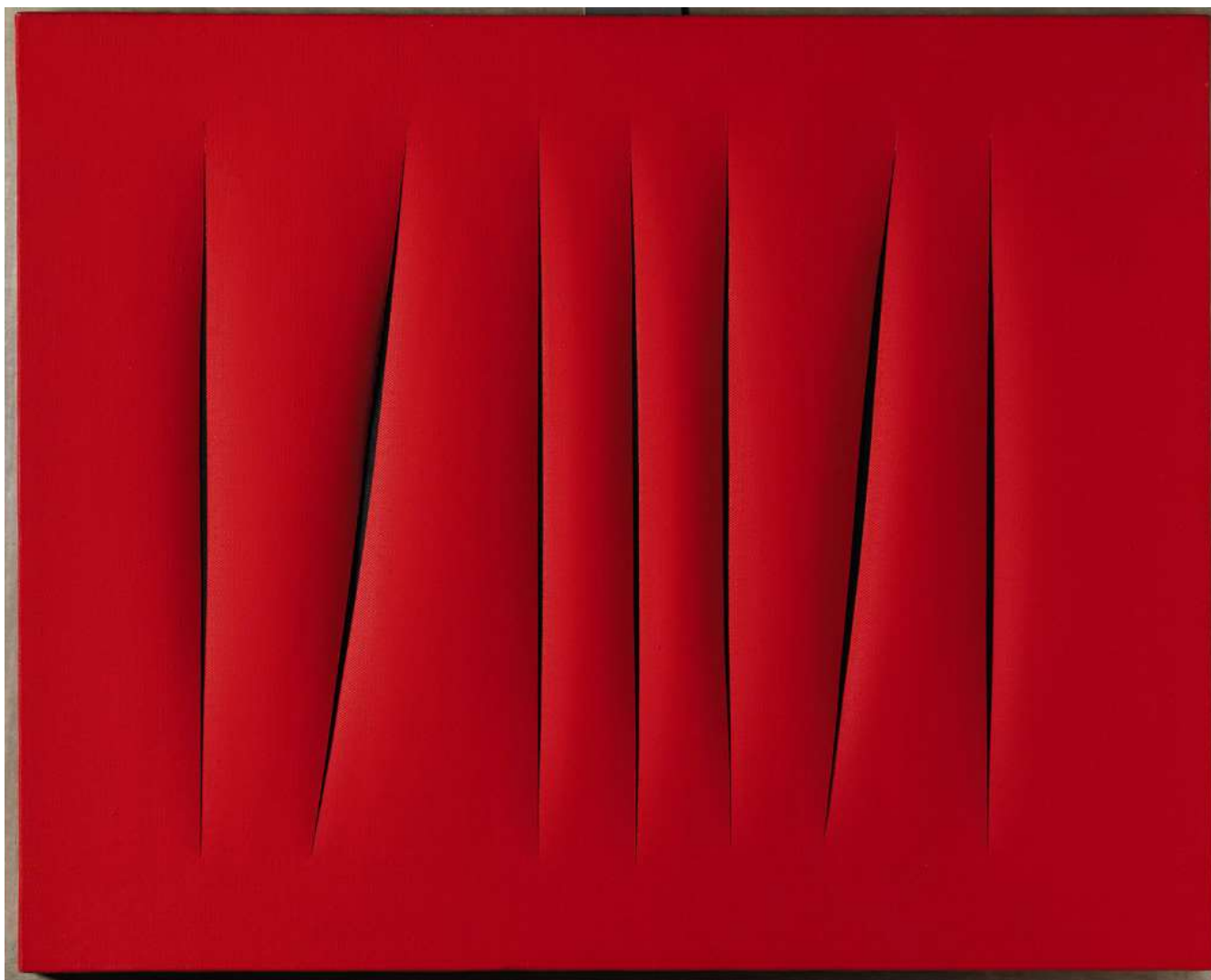
La storia delle epidemie e delle nostre difese.  
Tucidide, Lady Montagu, Manzoni, Roth:  
i racconti dei grandi scrittori

Lecture di Sonia Bergamasco e Neri Marcoré  
con il commento di Alberto Mantovani



Lecture immunologiche, da Tucidide a Camus: <https://www.repubblica.it/salute/dossier/noi-e-loro/>

**Fondazione Humanitas per la Ricerca e Piccolo Teatro di Milano:** Daniela Minerva, Claudio Longhi; lette da Sonia Bergamasco e Neri Marcoré, commento di Alberto Mantovani





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Science

RESEARCH ARTICLES

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Cite as: Q. Zhang *et al.*, *Science*  
10.1126/science.abd4570 (2020).

## **Inborn errors of type I IFN immunity in patients with life-threatening COVID-19**

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Science

RESEARCH ARTICLES

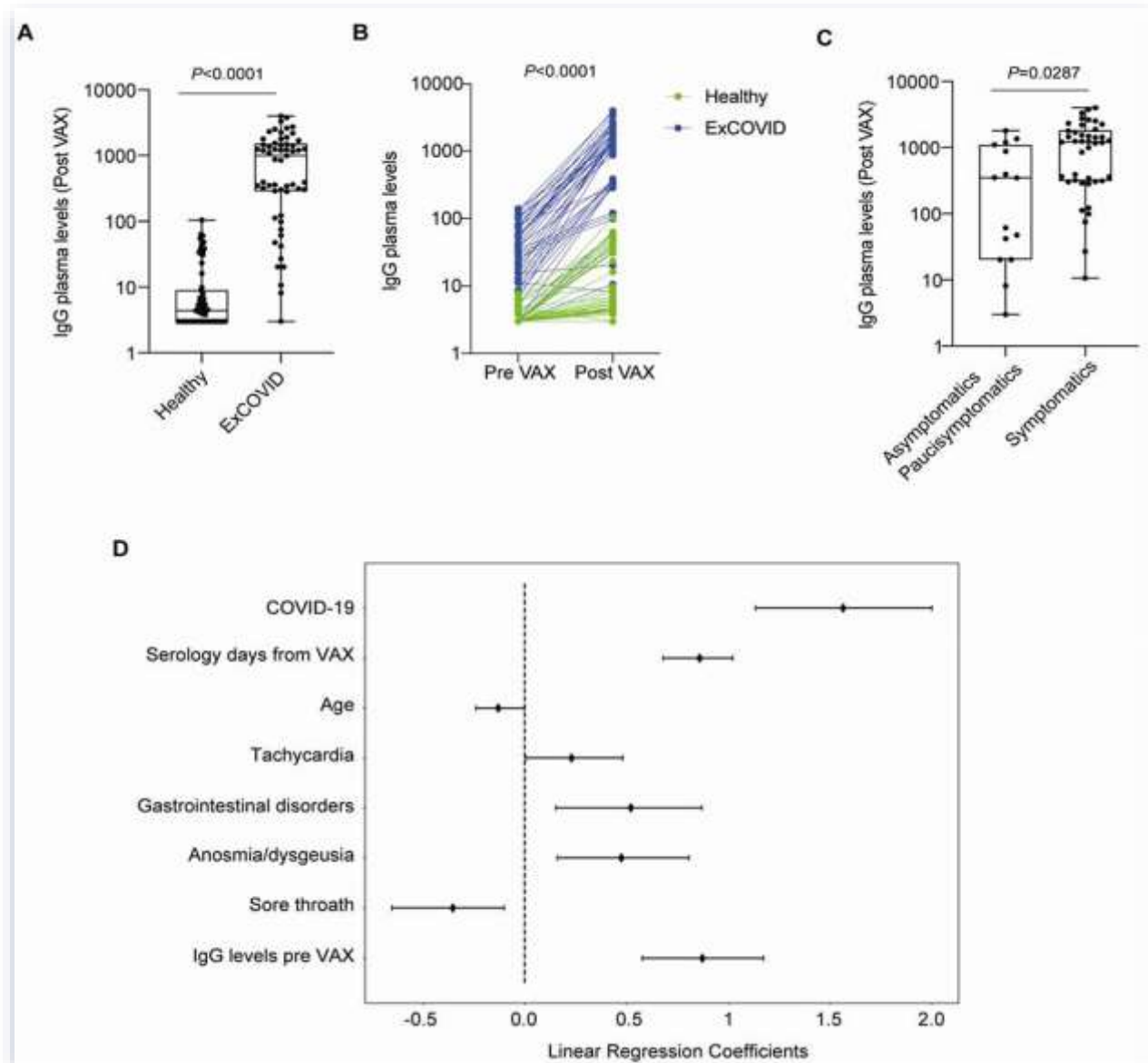
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Cite as: P. Bastard *et al.*, *Science*  
10.1126/science.abd4585 (2020).

## **Auto-antibodies against type I IFNs in patients with life-threatening COVID-19**

**COVID-19: AT THE INTERCEPTION OF GENETIC PREDISPOSITION, GENETIC IMMUNODEFICIENCY, AUTOIMMUNITY AND UNCONTROLLED INFLAMMATION**

# Ex COVID subjects increase exponentially anti-Spike 1/2 IgG levels after the first jab



(Levi, Azzolini, Pozzi .... Mantovani and Rescigno, MedRxiv, 2021)