COVID-19: esperti divisi (o no?) La scienza va in televisione e forse i cittadini cominciano a capire che è tutto molto complicato

Giuseppe Remuzzi

27 gennaio 2021

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

IL SENSO DI SORPRESA QUANDO L'EPIDEMIA DI COVID-19 È EMERSA È STATO IMMENSO: INCERTEZZA

1. Da dove arriva questo nuovo virus (c'è una prima evidenza che stava già circolando prima della comparsa in Wuhan)?
2. Perché gli uomini sono più suscettibili delle donne?
3. Perché le comunità etniche nere e minoritarie sono particolarmente a rischio?
4. Perché le persone che vivono nelle case di cura sono così vulnerabili?
5. Qual è la distanza di sicurezza da mantenere tra le persone in strada, sui trasporti pubblici o in coda al supermercato?
6. Indossare una mascherina può prevenire l'infezione o indossarla può essere un semplice gesto altruistico, riducendo il rischio che qualcuno venga infettato e poi passi il virus a qualcun altro?

7. Le scuole dovrebbero essere chiuse o, dal momento che I bambini sembrano avere un più basso rischio di sviluppare forme gravi di COVID-19, potrebbero rimanere aperte?

8. I governi dovrebbero chiudere i confini per prevenire l'ingresso del virus da altri paesi o questo costituisce un ulteriore rischio trascurabile, quando è già in corso una trasmissione dell'infezione nella comunità?

9. Dopo l'infezione, qual è lo stato di immunità dell'individuo e quanto dura?

10. Aver fatto il vaccino BCG protegge dallo sviluppare COVID-19?

11. Una pandemia può essere gestita da un' attenta e costante applicazione di igiene personale, distanziamento, e test a tappeto, tracciamento dei contatti e isolamento?

12. I lockdown sono davvero necessari?

13. In che modo il virus causa un tipo così insolito di polmonite, che è particolarmente diverso in molti pazienti da altri tipi di polmonite e sindrome da distress respiratorio acuto?

14. Le risposte immunitarie antivirali mediate dall'interferone sono benefiche o dannose per COVID-19?

15. Perché l'insufficienza renale è così importante?

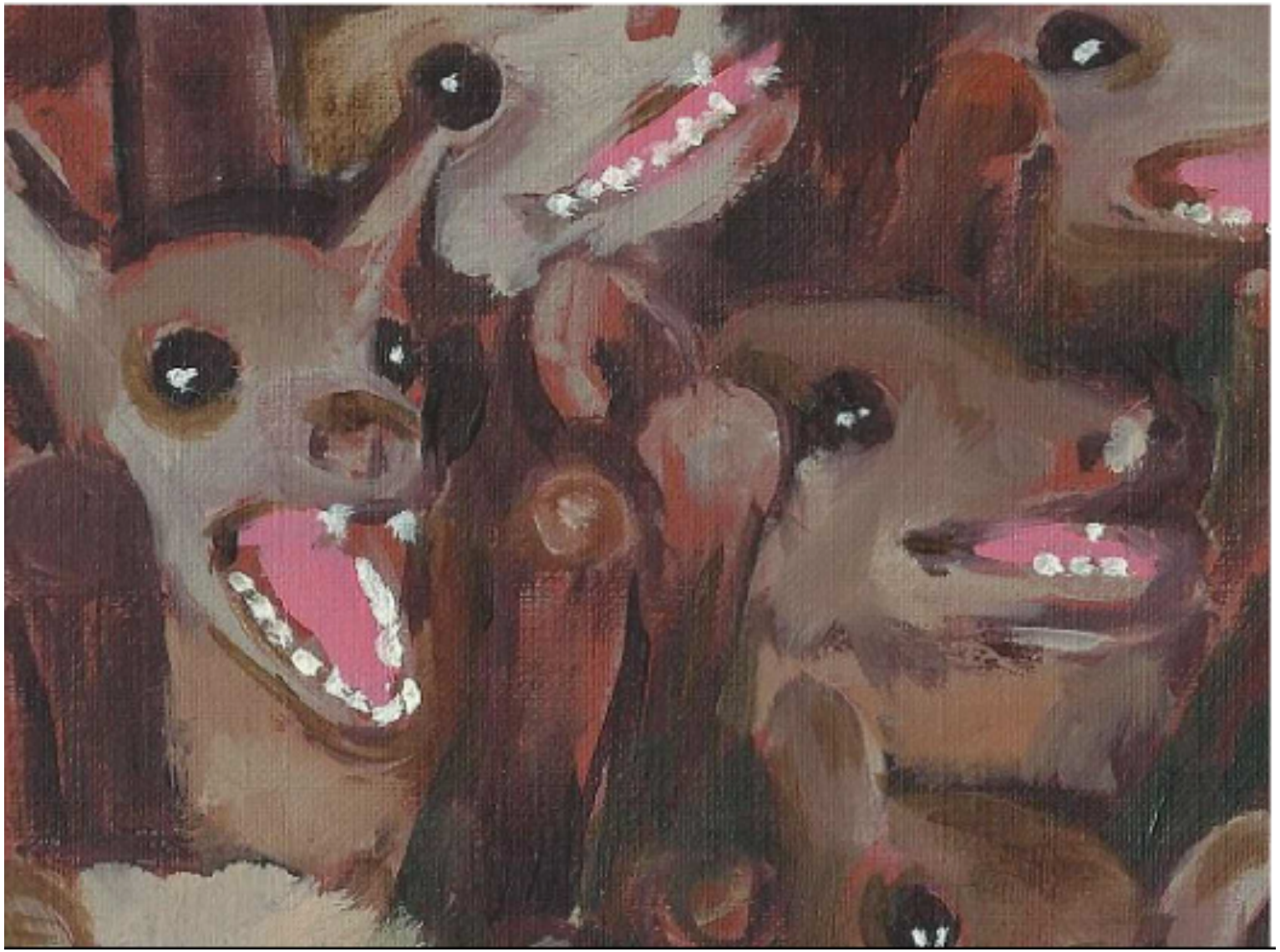
16. Qual è il responsabile della profonda coagulopatia trombotica osservata?

17. La malattia quanto dipende da trombosi microvascolare e dall'attivazione del complemento?

18. Ci sono dei buoni modelli animali per COVID-19?

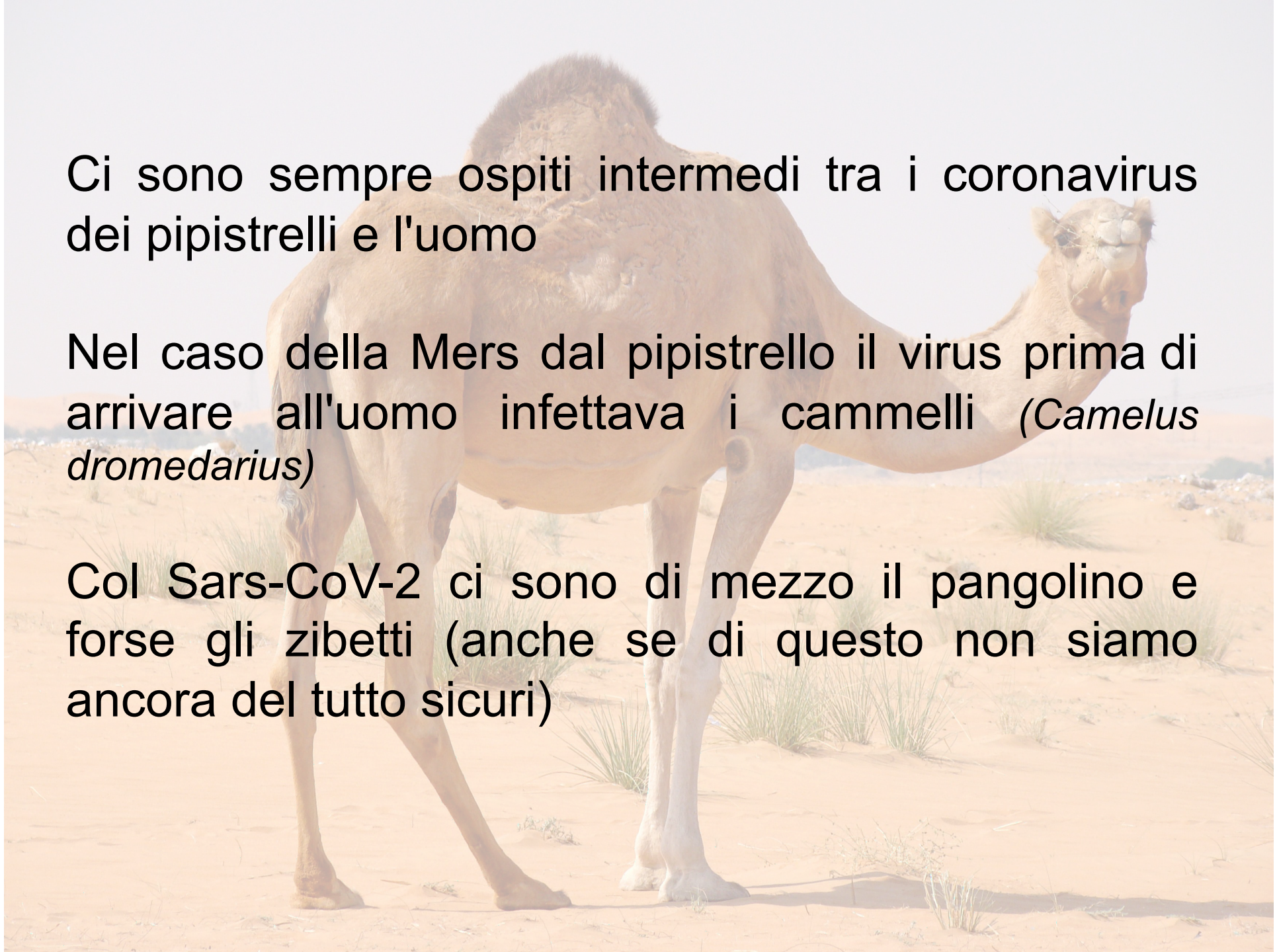

Hubei's Location in China Map
Russia
Mongolia
Beijing
North Korea
Japan
Hubei Province
Wuhan
India
Nepal
The Pacific Ocean
CHINA
Myanmar
Vietnam
Laos
Thailand
Philippines
N
500 km


广西野生水鱼



I coronavirus convivono con i pipistrelli da milioni di anni, incluso, certamente, ma non solo, il Sars-CoV-2, quello del Covid19, la malattia che finora ha infettato 100 milioni di persone al mondo (ma potrebbero essere molte di più) e ne ha ucciso più di 2 milioni

Non è il primo coronavirus dei pipistrelli che arriva all'uomo e porta malattie: prima c'è stato quello della Sars nel 2003 che ha causato più di ottomila casi e quasi 800 morti e poi nel 2012 sempre dai pipistrelli arriva il coronavirus della Mers la Sindrome respiratoria del Medio Oriente che ha infettato 2.500 persone nel 2012 uccidendone una su tre



Ci sono sempre ospiti intermedi tra i coronavirus dei pipistrelli e l'uomo

Nel caso della Mers dal pipistrello il virus prima di arrivare all'uomo infettava i cammelli *(Camelus dromedarius)*

Col Sars-CoV-2 ci sono di mezzo il pangolino e forse gli zibetti (anche se di questo non siamo ancora del tutto sicuri)

Nature · 11 NOVEMBER 2020

Where did COVID come from? WHO investigation begins but faces challenges

Identifying the source will be tricky, and investigators will need to grapple with the sensitive political situation

Smriti Mallapaty

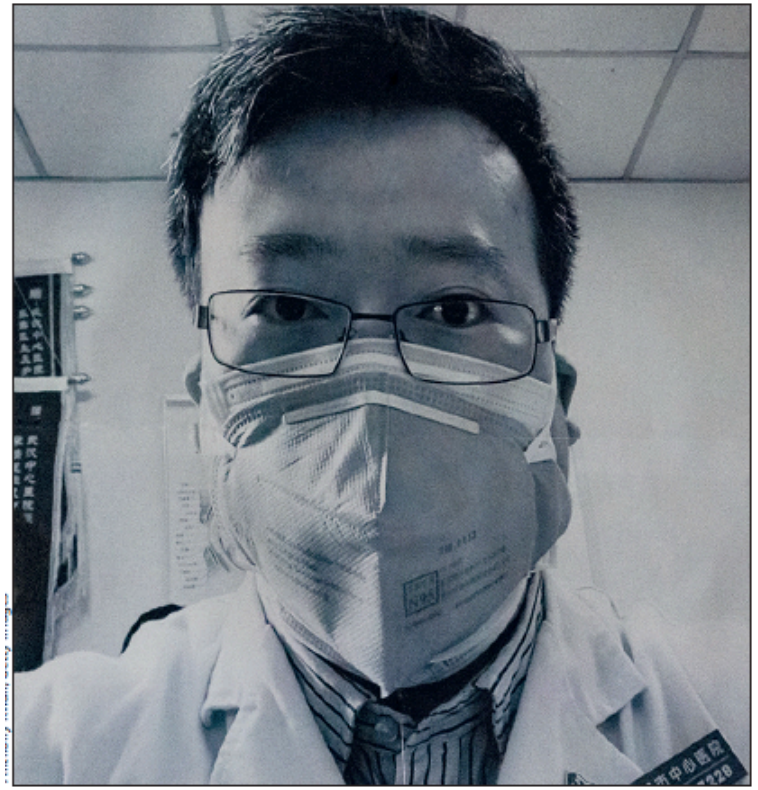
- We know some of these early cases seem to be linked to the live markets in Wuhan. But some were not
- We don’t really understand the lines of transmission of the virus in those early days
- There’s clearly a connection between wildlife, the environment, the urban setting. But we don’t really know where the pieces of that puzzle are or how the pieces of that puzzle join

Li Wenliang lavorava come oftalmologo a Wuhan. Il 30 dicembre, tramite il suo account WeChat, ha avvertito privatamente amici e colleghi medici sull'esistenza del nuovo virus SARS

Quando i suoi post online sono trapelati, è stato arrestato, interrogato e ammonito per diffondere pettegolezzi

Li è stato costretto a firmare una dichiarazione in cui confermava che avrebbe smesso di diffondere queste presunte voci

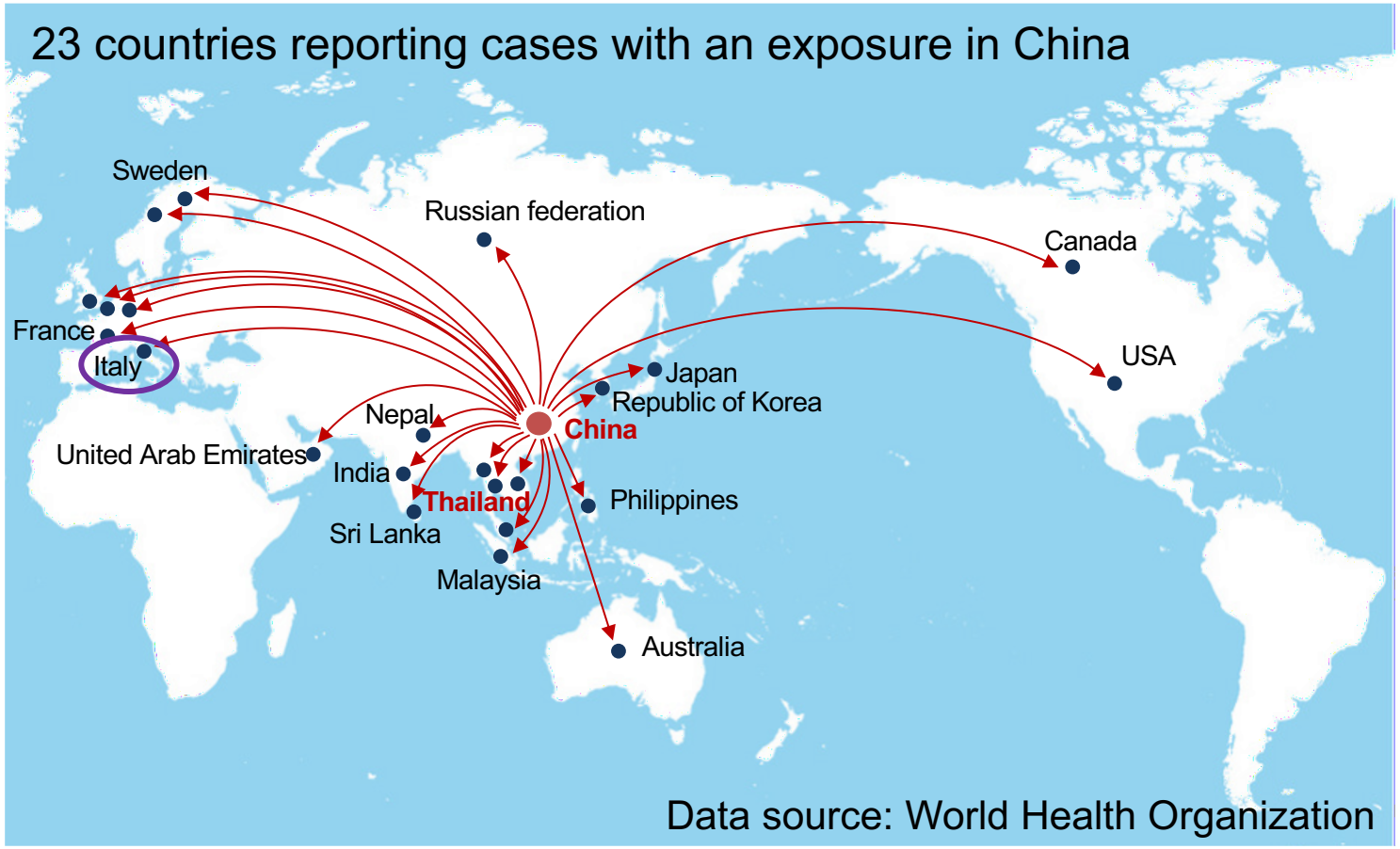
Ai funzionari locali del Partito Comunista in Cina piace mantenere un basso profilo con Pechino. Il loro compito principale è preservare l'ordine pubblico e la stabilità



Li Wenliang

Ophthalmologist who warned about the outbreak of COVID-19. Born in Beizhen, China, on Oct 12, 1986, he died after becoming infected with SARS-CoV-2 in Wuhan, China, on Feb 7, 2020, aged 33 years.

INTERNATIONAL EXPORTED COVID-19 CASES AS OF 12 FEBRUARY 2020



Wuhan is a major domestic and international transport hub

Flights out of Wuhan carried passengers to Bangkok, Hong-Kong, Seoul, Singapore, Tokyo, Taipei, Kuala Lumpur, Sydney, Melbourne and London

It was no accident that the first reported case of infection outside of China was in Thailand

The Guardian – 13 March 2020

First Covid-19 case happened in November, China government records show – report

The report, in the South China Morning Post, said Chinese authorities had identified at least 266 people who contracted the virus last year and who came under medical surveillance, and the earliest case was 17 November – weeks before authorities announced the emergence of the new virus

Newscientist – 06 May 2020

Covid-19 news: Europe's first case may have been in December

New York Times - 06 May 2020

New Report Says Coronavirus May Have Made Early Appearance in France

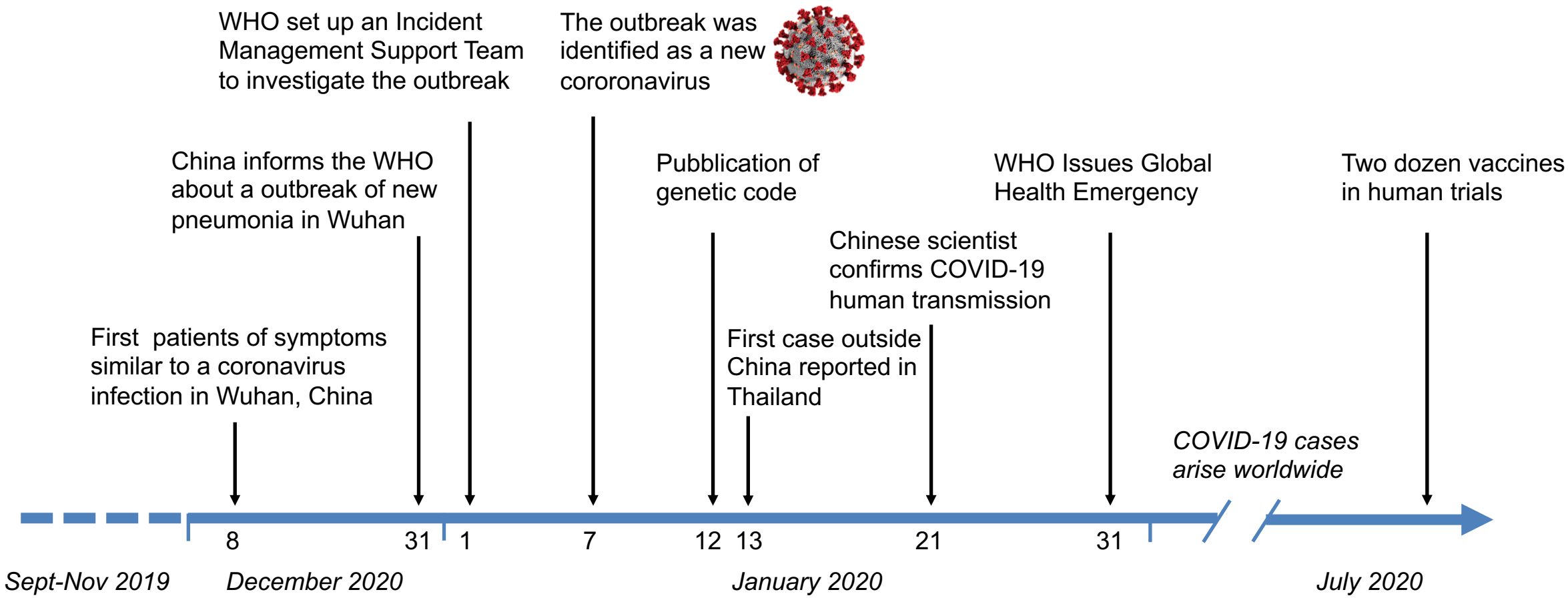
The Guardian – 9 June 2020

Coronavirus may have been in Wuhan in August, study suggests

Sciencedaily – 11 September 2020

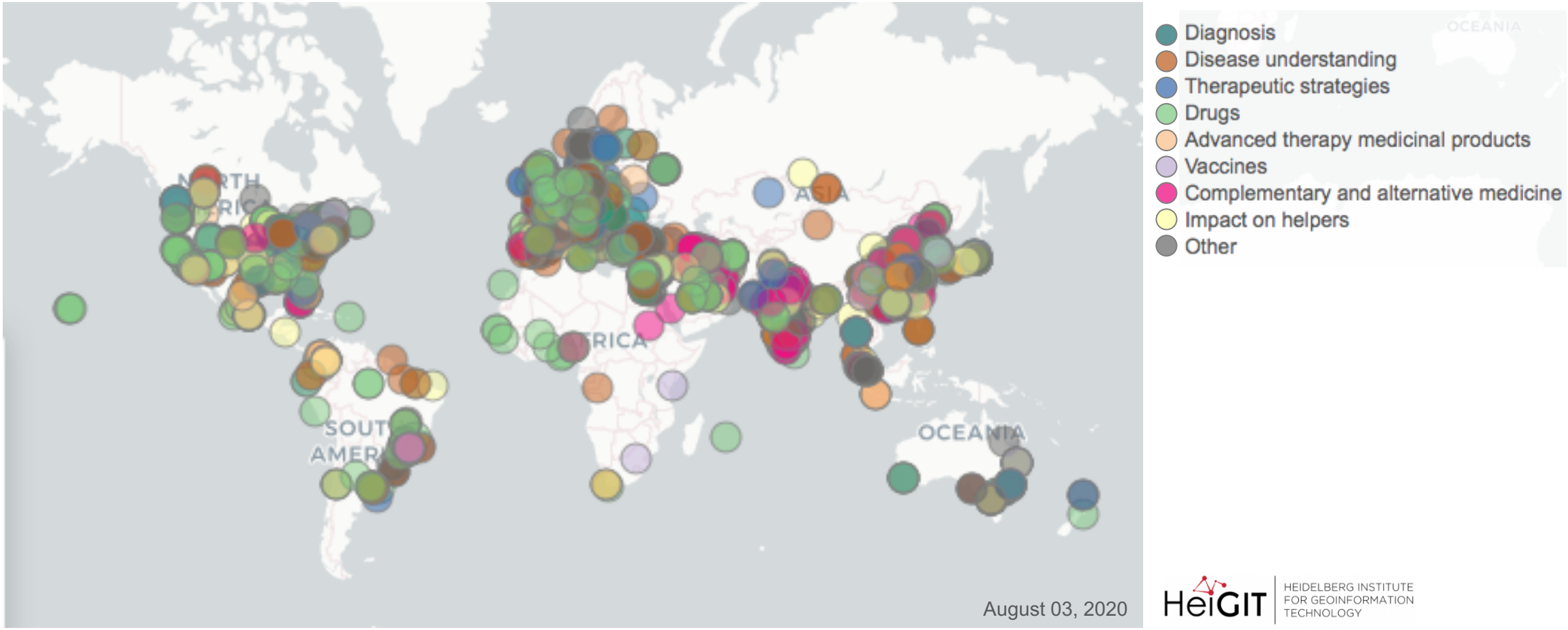
COVID-19 may have been in LA as early as last December, study suggests

CORONAVIRUS TIMELINE: TRACKING THE CRITICAL MOMENTS OF COVID-19



MAPPING COVID-19 RESEARCH

The "Map of Hope" provides a geographical overview of planned, ongoing and completed studies



HeiGIT HEIDELBERG INSTITUTE FOR GEOINFORMATION TECHNOLOGY

Lancet, Published Online January 24, 2020

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Chaolin Huang, Yeming Wang*, Xingwang Li*, Lili Ren*, Jianping Zhao*, Yi Hu*, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang†, Bin Cao†*

The 2019-nCoV infection caused clusters of severe respiratory illness similar to severe acute respiratory syndrome coronavirus and was associated with ICU admission and high mortality

- Baseline characteristics of patients
- Timeline of symptoms after onset of illness
- All possible laboratory measurements
- X Ray and TC examination

Possiamo davvero credere a quello che dicono?

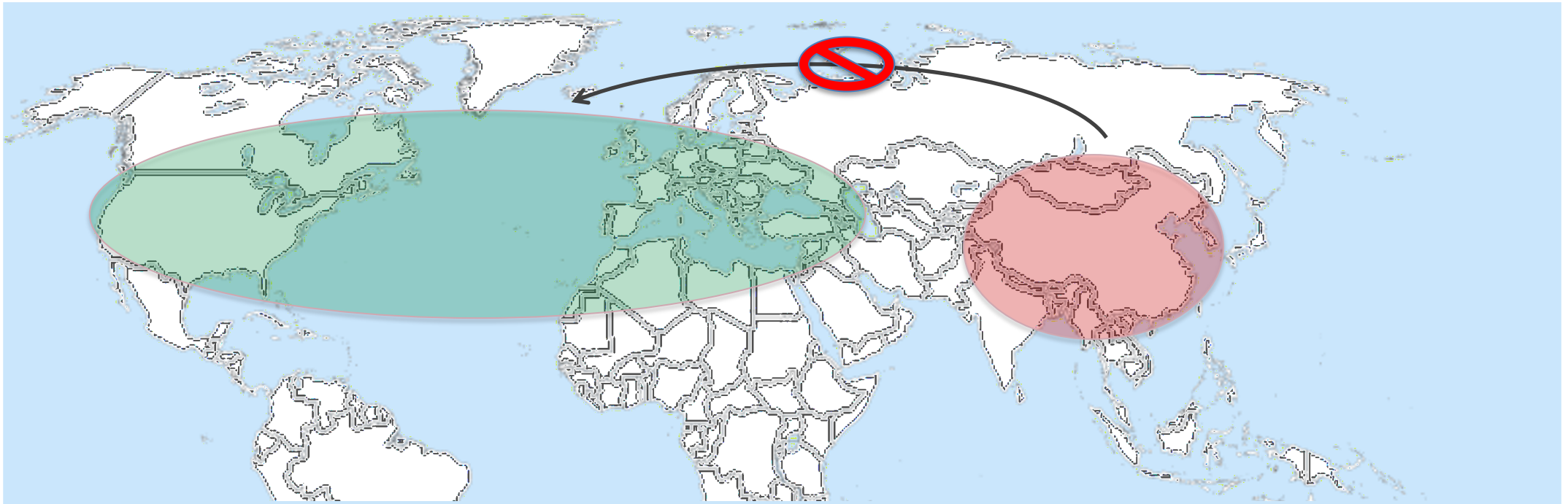
Sono davvero in grado di gestire questi pazienti?

DOMANDE CHE AVREMMO DOVUTO FARCI SE I LAVORI CINESI FOSSERO STATI PRESI SERIAMENTE

- Abbiamo dispositivi di protezione individuali?
- Come possiamo gestire il distanziamento?
- Qual è la nostra policy nelle scuole?
- Come possiamo fermare la trasmissione del virus nelle comunità?

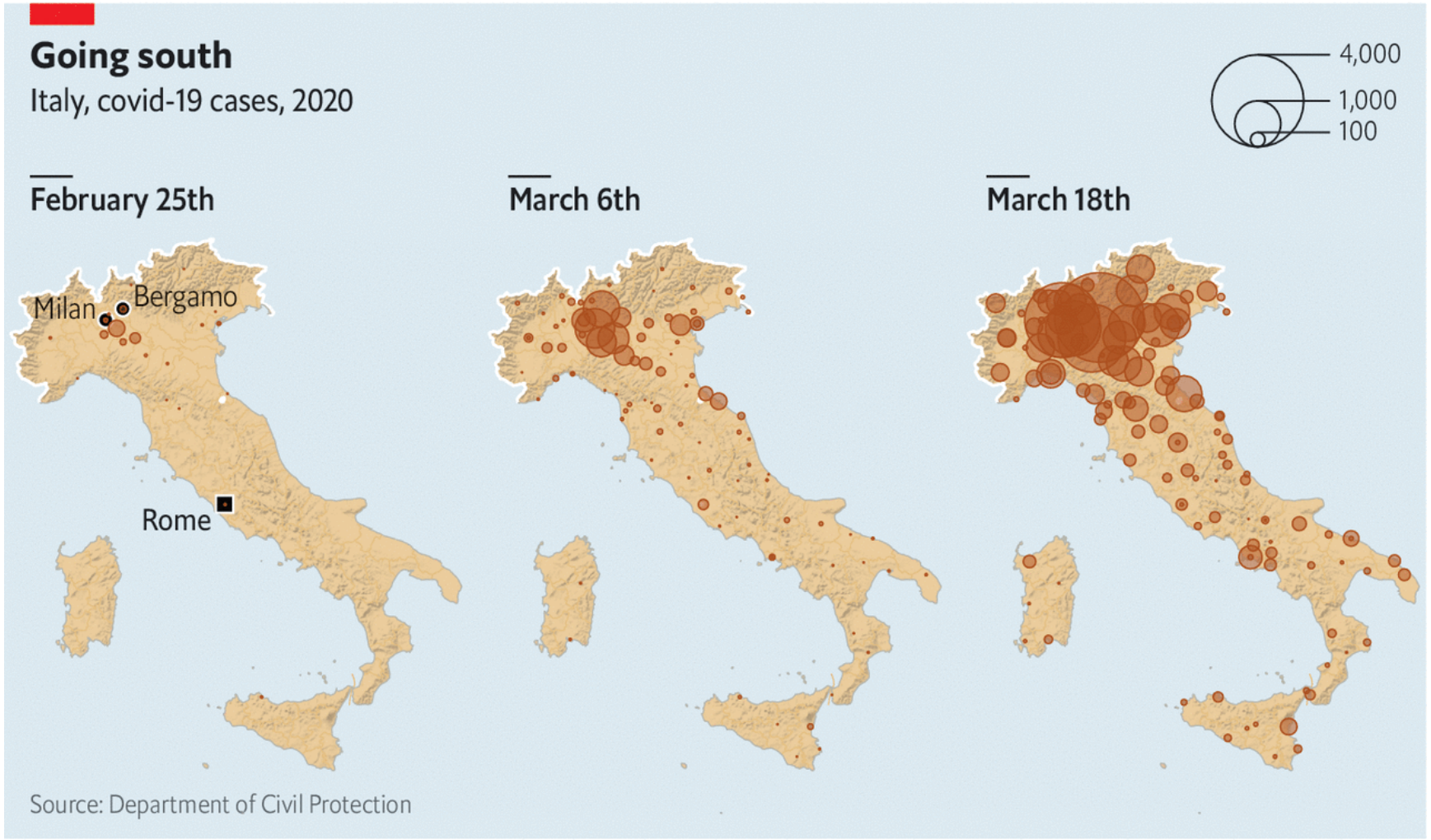
Tutto questo avrebbe dovuto essere discusso entro le prime 48-72 ore dopo la dichiarazione dell'emergenza

Non è successo



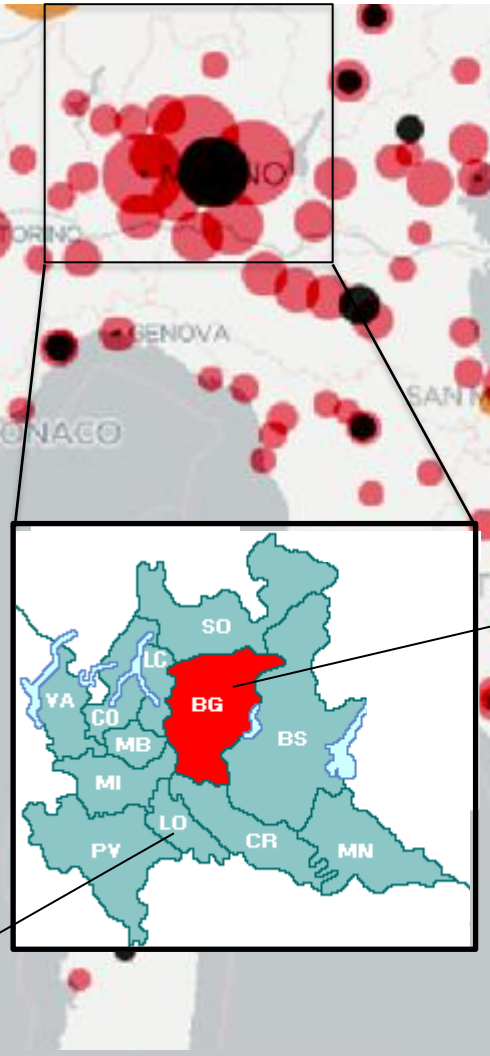
It wasn’t just Italy, it was all of Europe and North America

The Western scientists didn’t take the science coming out of China seriously



The Economist

June 29, 2020



Alzano Lombardo (BG), first documented cases on February 23first, 2020.

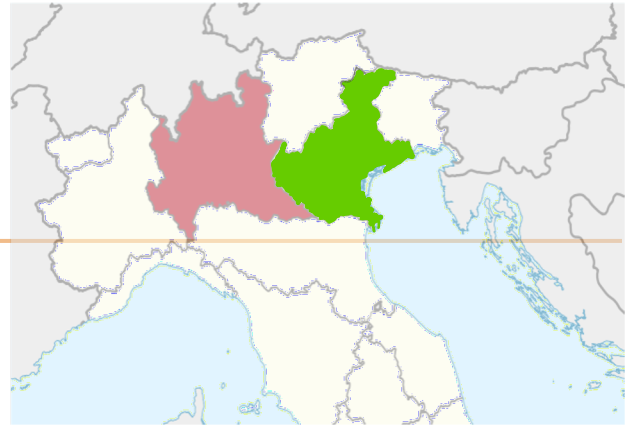
Lodi, first reported community-acquired COVID-19 case in Italy on 20th February, 2020.

The New York Times

THE LOST DAYS THAT MADE BERGAMO A CORONAVIRUS TRAGEDY

By Jason Horowitz Photographs by Fabio Bucciarelli
Nov. 29, 2020

Lombardia o Veneto?



Il Veneto ha fatto bene, ma sono stati anche fortunati

Un calcolo (che si chiama ‘replicazione diagnostica’ (RD_t)*, effettuato dall’epidemiologo Cesare Cislaghi, dimostra come all’inizio ci fossero molti più contagi nell’area lombarda, ma dopo una primissima fase la Lombardia è riuscita a ottenere un calo più rapido dell’epidemia rispetto al Veneto: dopo circa un mese il suo valore di replicazione era 2,3, in Veneto era 3 nonostante quello lombardo fosse un focolaio molto ampio

La materia è complessa

* replicazione diagnostica: misura la proporzione di casi notificati dopo un certo numero di giorni dai precedenti, è un indice che stima con buona approssimazione l’indice Rt che serve per misurare l’intensità delle riproduzioni delle infezioni dopo un certo tempo medio di generazione del contagio

EBioMedicine 61 (2020) 103069

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

COVID-19 and lombardy: TESTing the impact of the first wave of the pandemic

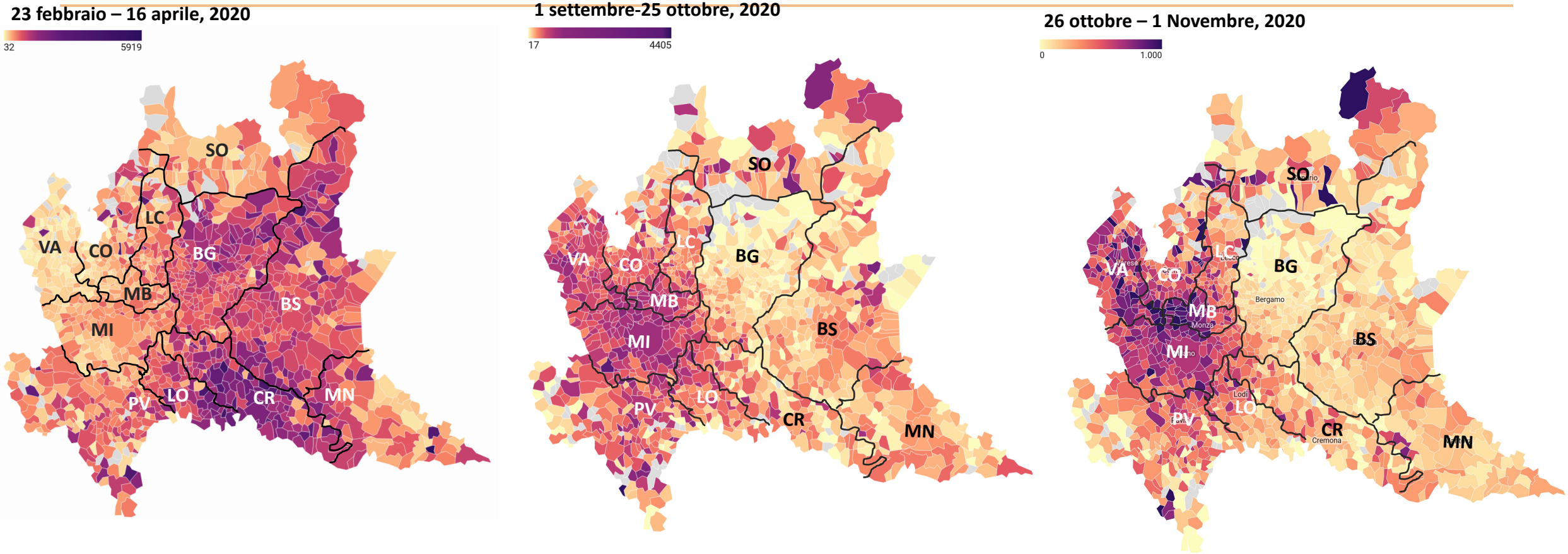
Luca Perico[a,1], Susanna Tomasoni[a,1], Tobia Peracchi[a], Annalisa Perna[a], Anna Pezzotta[a], Giuseppe Remuzzi[a,b,*], Ariela Benigni[a]

[a] Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Bergamo, Italy
[b] Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy

LO STUDIO DEL MARIO NEGRI SULLA CIRCOLAZIONE DEL VIRUS A BERGAMO E PROVINCIA

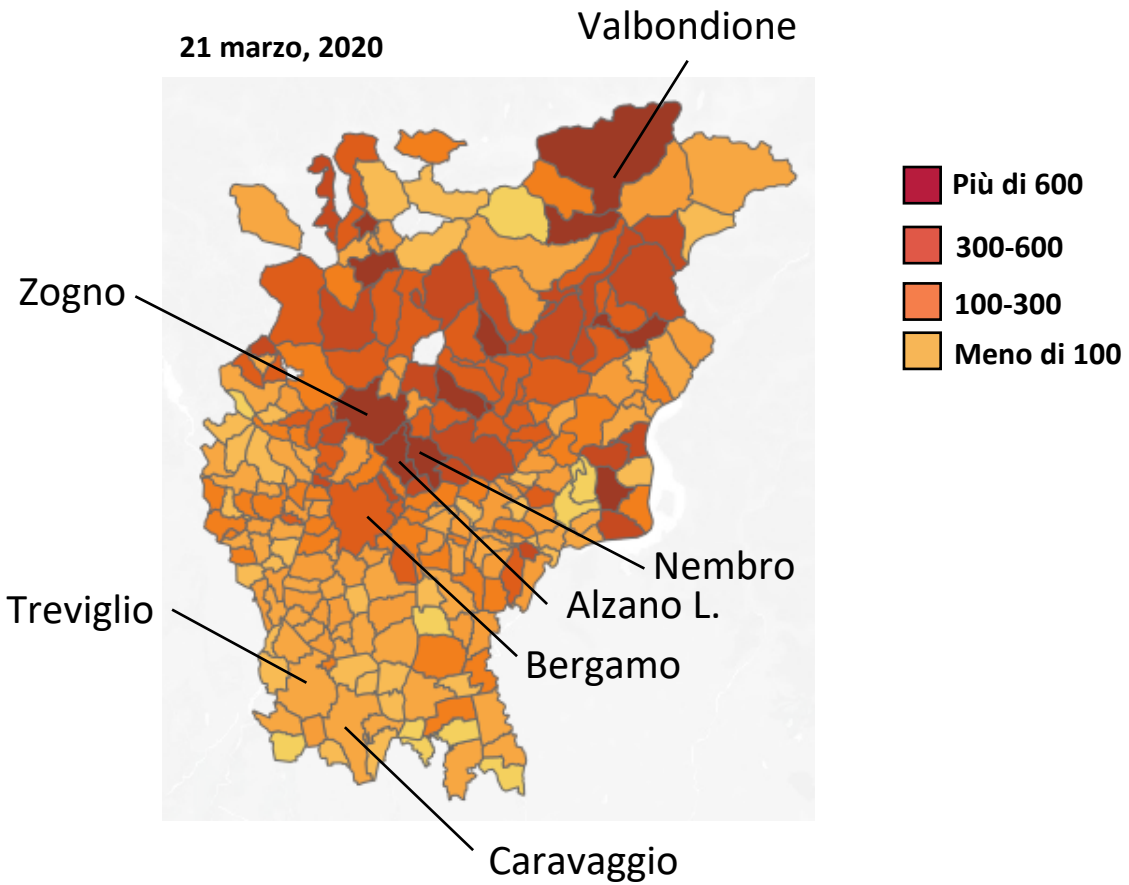
- 431 volontari testati: 133 ricercatori del Mario Negri e 290 dipendenti della Brembo.
- Il 38,5% dei volontari è risultato positivo al test sierologico ed ha sviluppato gli anticorpi contro il SARS-CoV-2.
- Bergamo si profila come una delle aree più colpite al mondo con una sieroprevalenza che supera di gran lunga le stime di New York(19.9%), Londra (17.5%) e Madrid (11.3%).
- Se si estende il dato del campione a tutta la popolazione della provincia di Bergamo, si può ipotizzare una circolazione del virus che arriva a toccare le 420 mila unità, contro le quasi 16.000 segnalate al 25 settembre 2020.
- Ciò indicherebbe che il 96% delle infezioni da COVID-19 non è stato rilevato dal sistema sanitario.

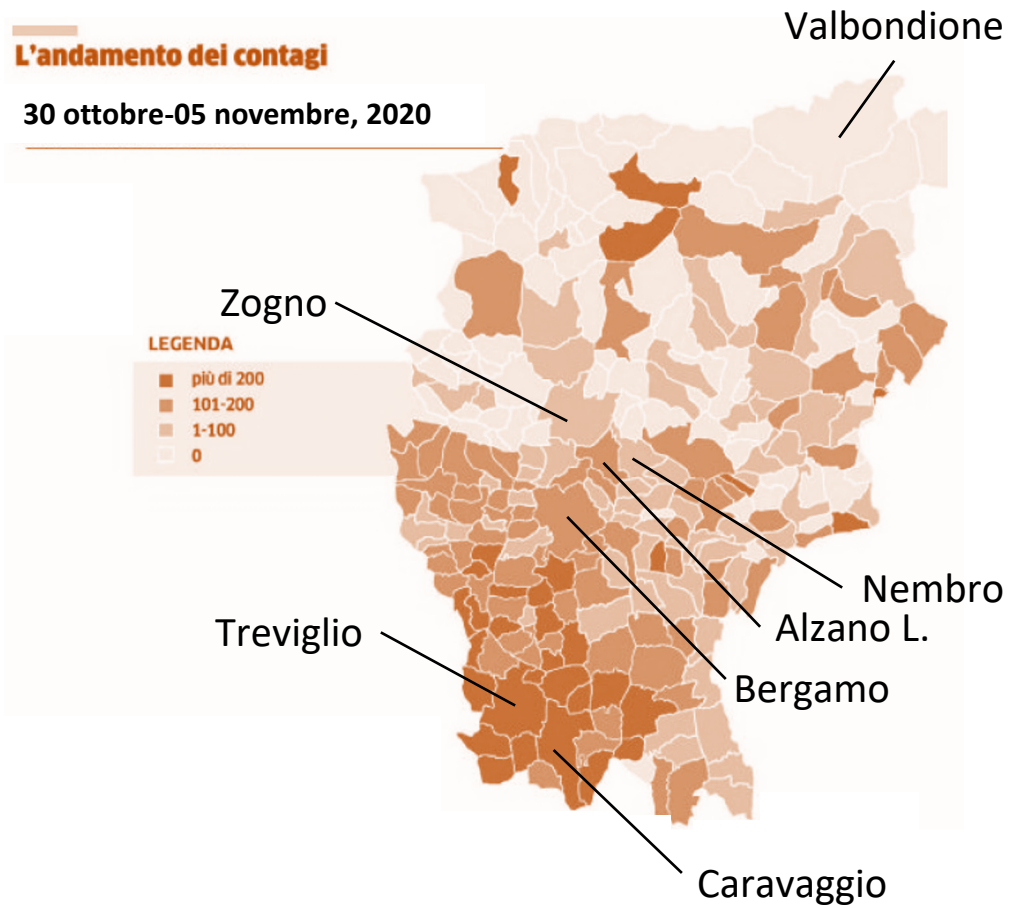
Incidenza di nuovi casi (per 100.000 abitanti) di COVID-19 in Lombardia



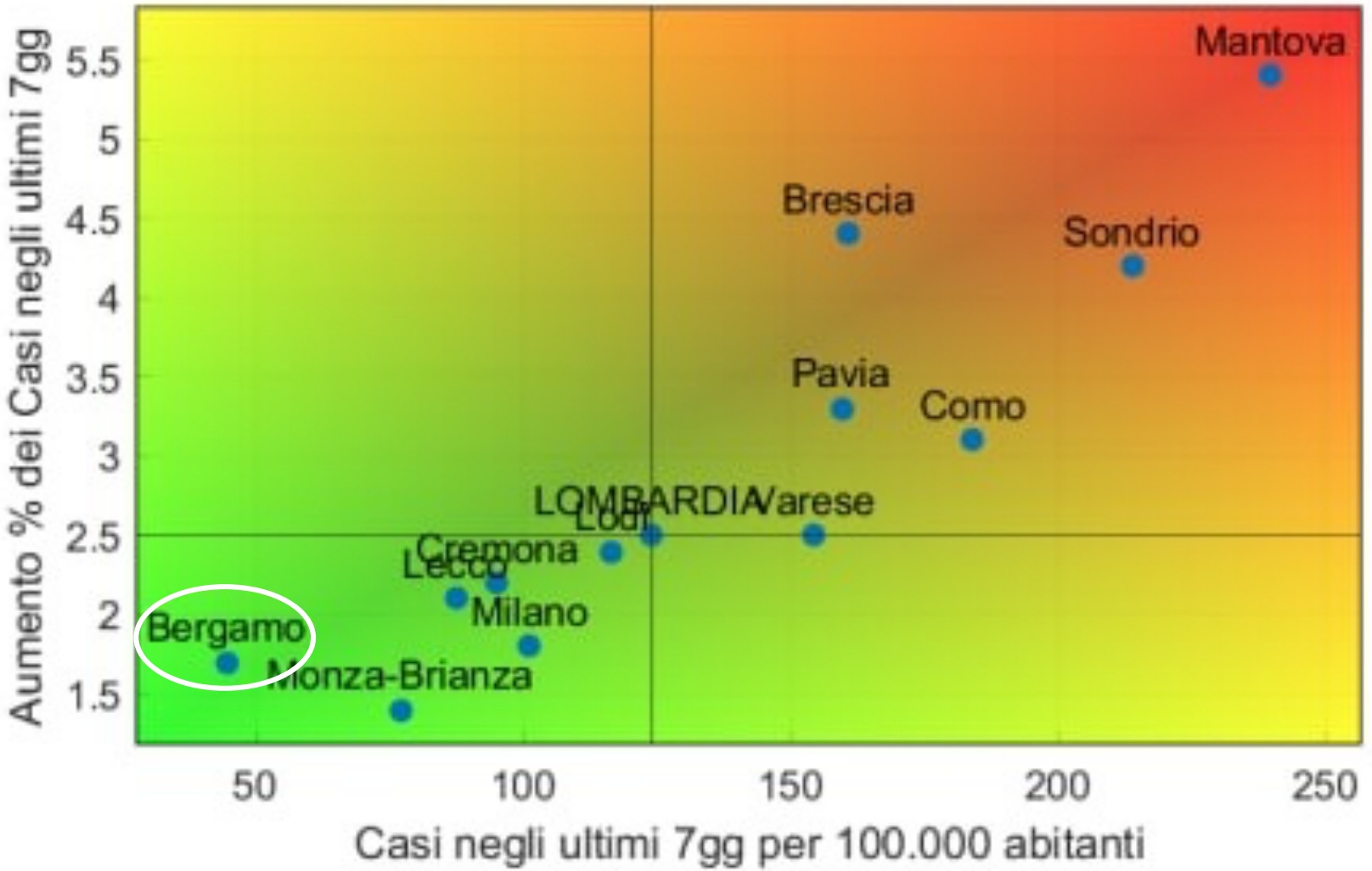
Andamento dell'incidenza di nuovi casi di COVID-19 ogni 100.000 nei diversi comuni della Lombardia a partire dal 23 Febbraio 2020 all'1 Novembre, 2020

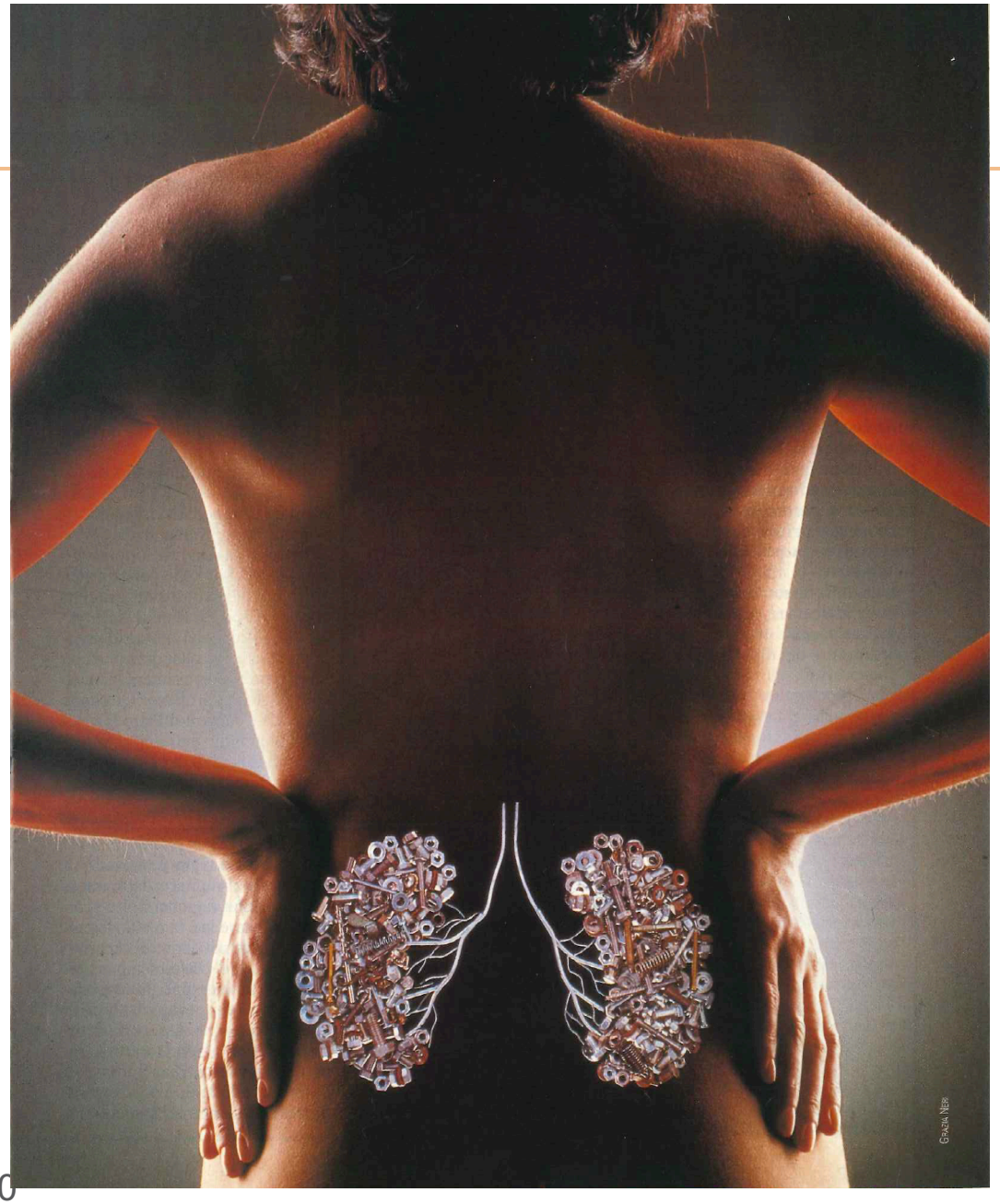
Incidenza di nuovi casi (per 100.000 abitanti) di COVID-19 nella Provincia di Bergamo



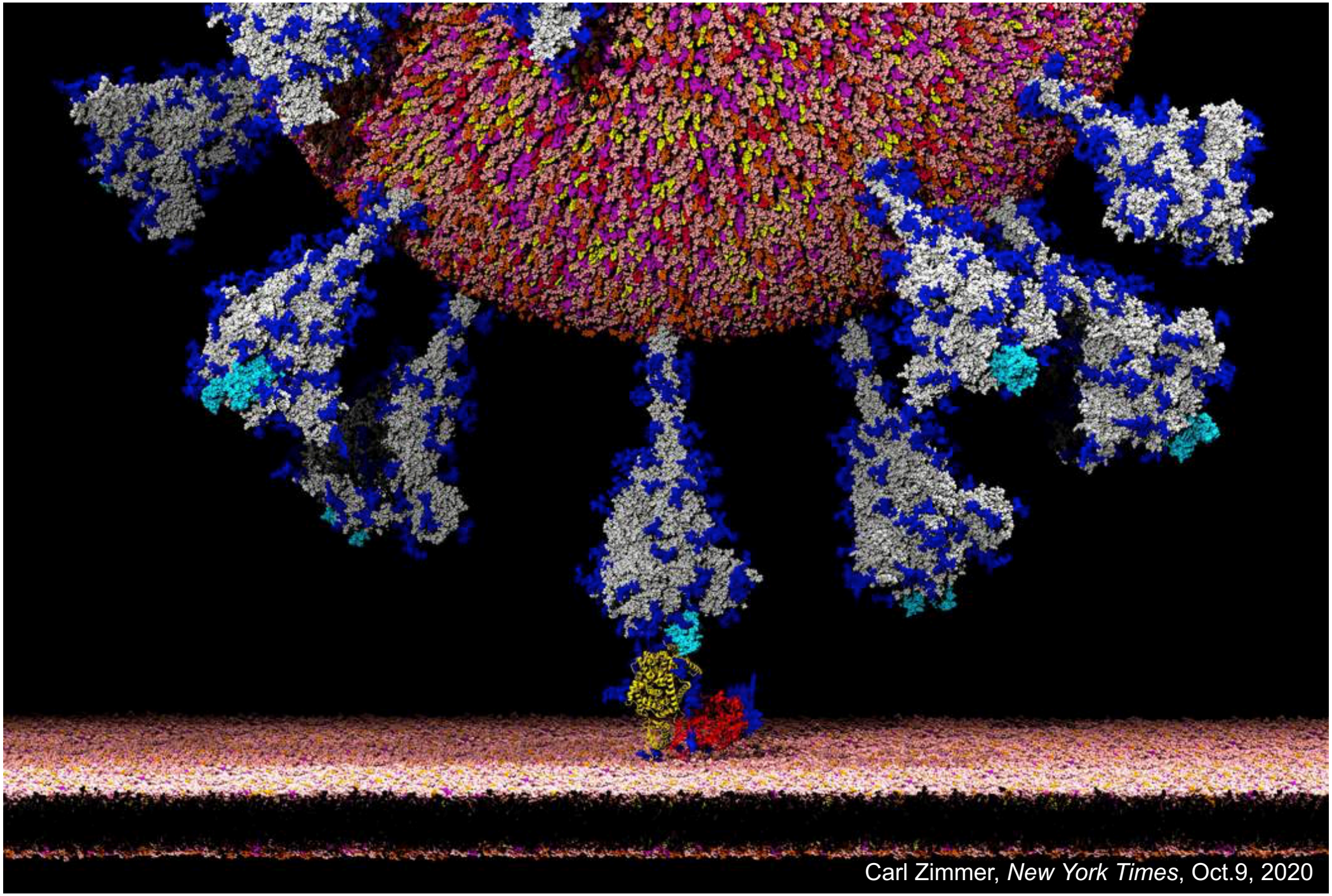


Confronto dell'incidenza di nuovi casi di COVID-19 ogni 100.000 nei diversi comuni della Bergamasca tra il 14 marzo e il 05 novembre, 2020.



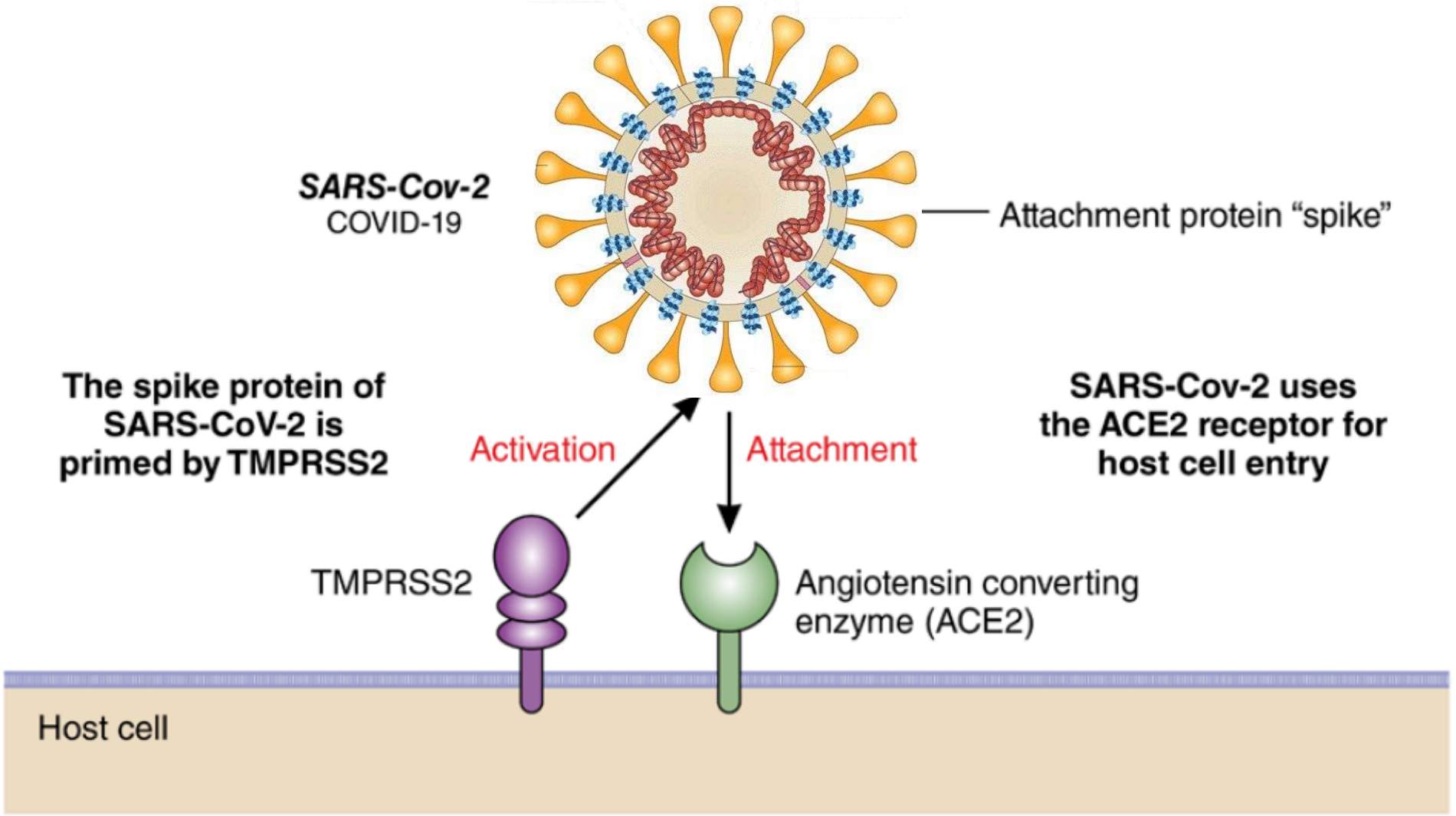


“Perché mai i nefrologi dovrebbero occuparsi di Coronavirus?”



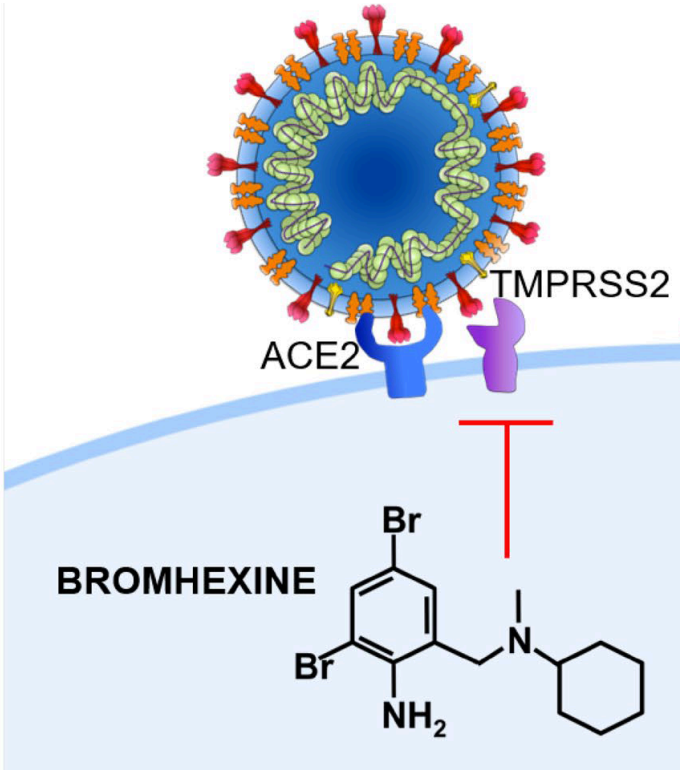
Carl Zimmer, *New York Times*, Oct.9, 2020

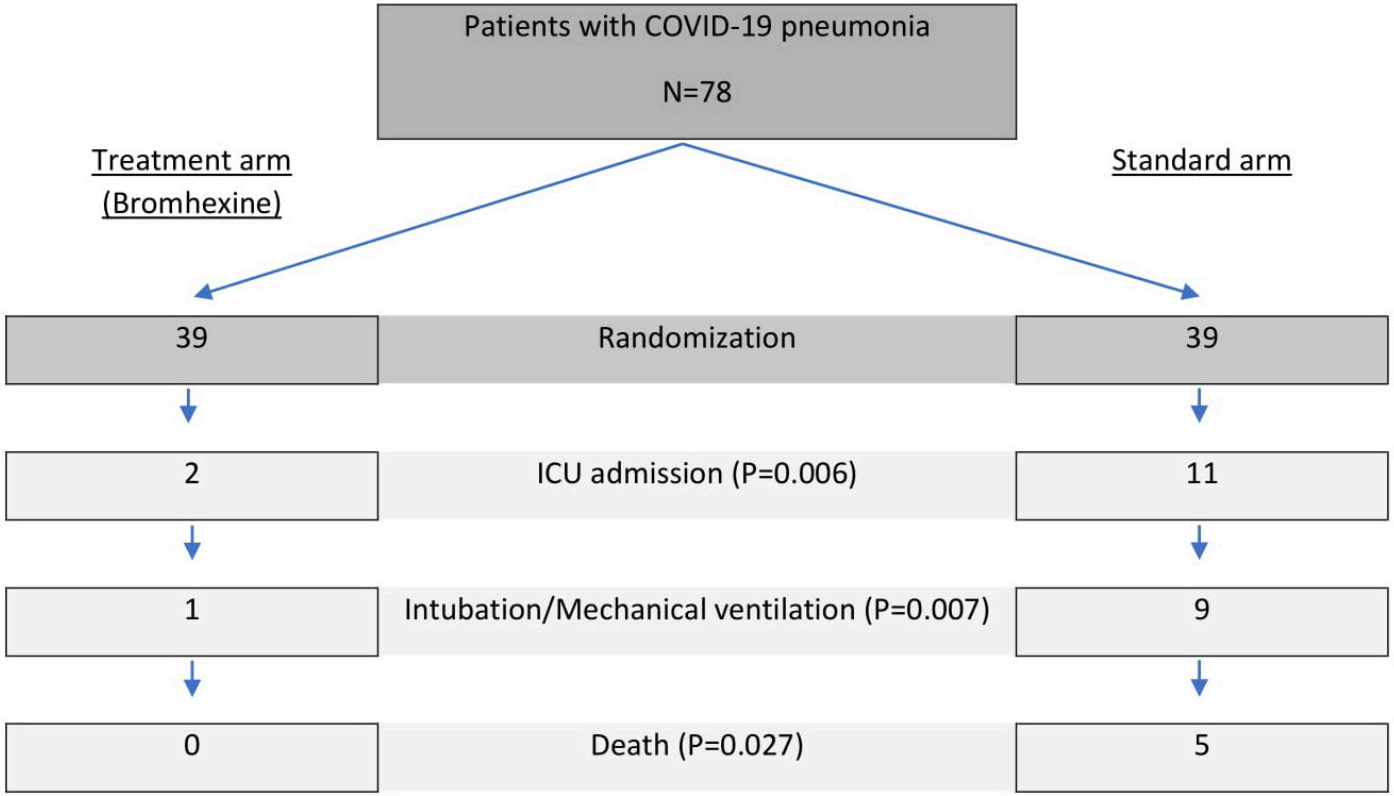
SARS-COV-2 BINDS TO THE ANGIOTENSIN-CONVERTING ENZYME 2 (ACE2) RECEPTOR AFTER ACTIVATION OF THE SPIKE PROTEIN BY TRANSMEMBRANE PROTEASE SERINE 2 (TMPRSS2)



Clerkin et al., *Circulation,* 2020

EFFECT OF BROMHEXINE ON CLINCIAL OUTCOMES AND MORTALITY IN COVID-19 PATIENTS: A RANDOMIZED CLINICAL TRIAL





Ansarin et al., *Bioimpacts,* 2020

CLINICAL STUDIES FOR BROMHEXINE

- Use of Bromhexine for prevention of infection and incidence of COVID-19 in Medical Personnel assisting patients with new coronavirus disease	Almazov National Medical Research Centre, Saint Petersburg, Russian Federation
- Bromhexine: a novel regimen for COVID-19 prophylaxis in healthcase professionals	National Institute of Rehabilitation, Mexico City, Cdmx, Mexico
- Evaluating the efficacy and safety of Bromhexine hydrochloride tablets combined with standard treatment/standard treatment in patients with suspected and mild novel coronavirus pneumonia (COVID-19)	The Second Affiliated Hospital of Wenzhou, Medical University Wenzhou, Zhejiang, China
- Use of Bromhexine for treatment of COVID-19 pneumonia	SB Celje, Celje, Slovenia
- Bromhexine and spironolactone for coronavirus infection requiring hospitalization	Lomonosov Moscow State University Medical Research and Educational Center Moscow, Moscow Region, Russian Federation

Clinicaltrials.gov, November 25, 2020

THE CLINICAL PRESENTATION OF COVID-19

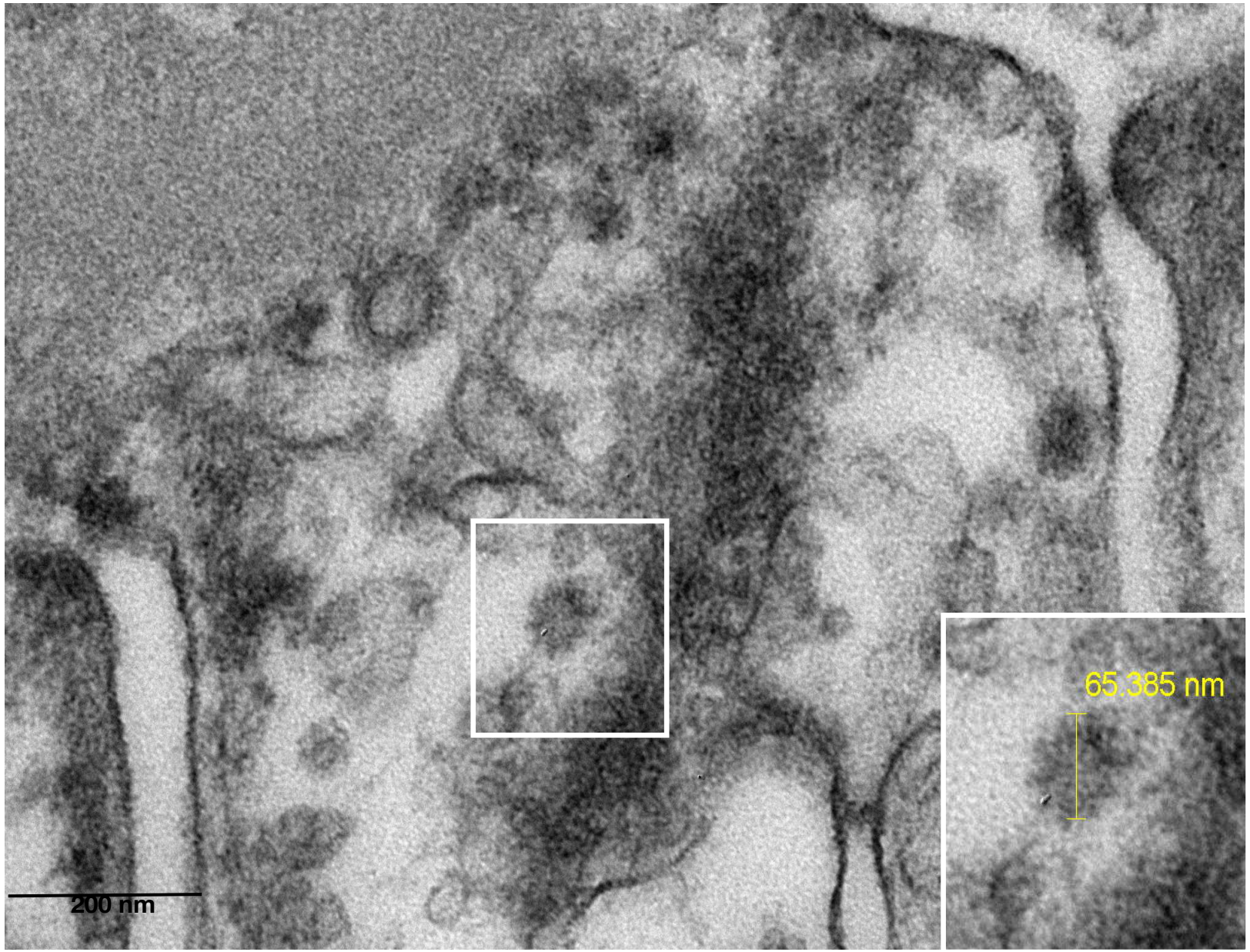
- For about 80% of infected patients, COVID-19 is a mild disease that is mostly restricted to the upper and conducting airways, characterized by modest symptoms, similar to the common flu, including fever and a dry cough, which resolve spontaneously after 6 to 10 days

- In the remaining 20% of patients, SARS-CoV-2 spreads in the lungs, where it attacks the alveoli. These patients develop severe illness characterized by atypical interstitial bilateral pneumonia and acute respiratory distress syndrome, and 10% of these subjects subsequently die

Those with acute kidney injury were more than five times as likely to die as COVID-19 patients without it

If these folks are not dying of lung failure, they're dying of renal failure

Wadman et al., Science, 2020



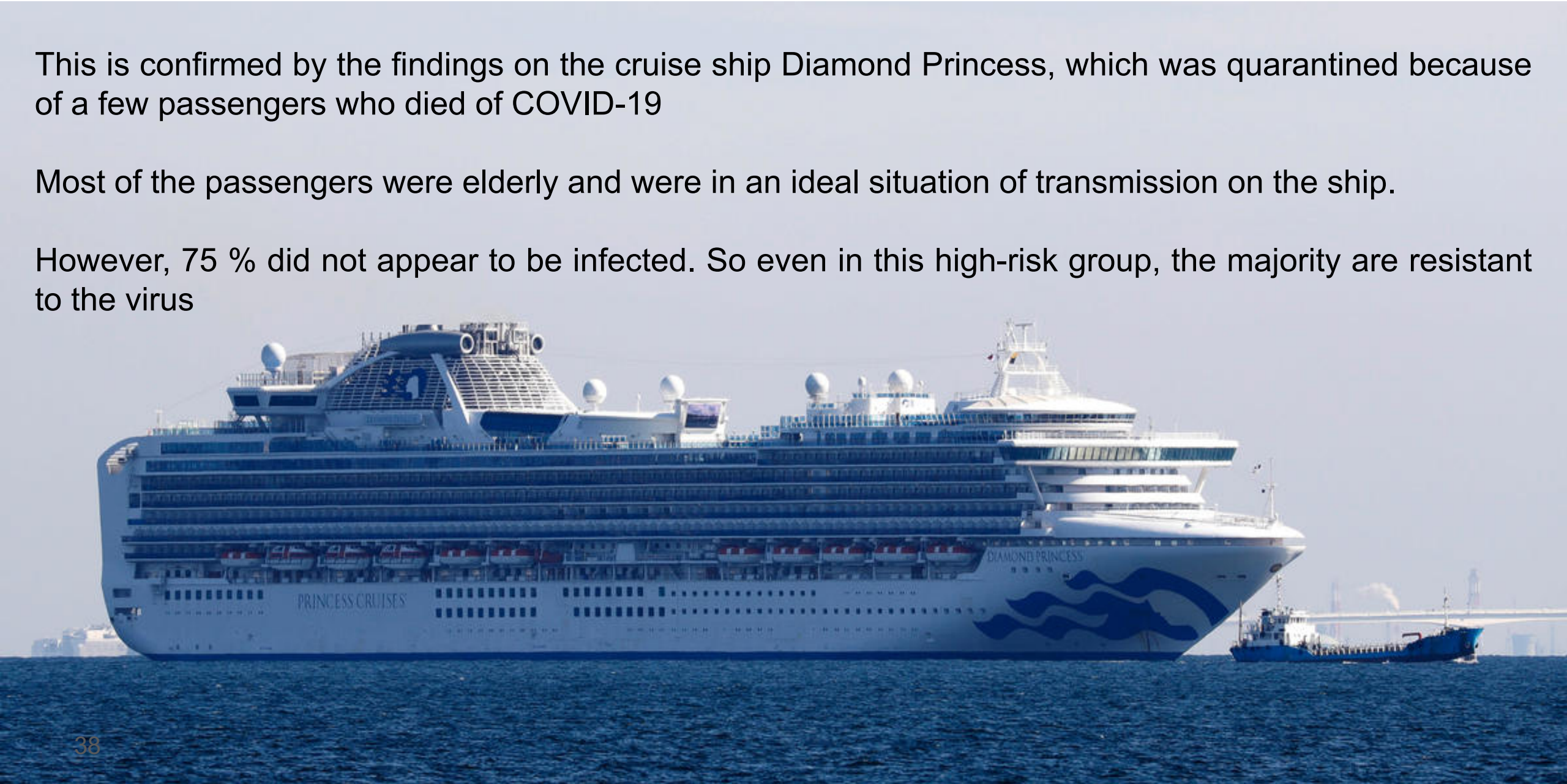
Mauro Abbate, Daniela Rottoli, Andrea Gianatti, *Nephron,* 2020

It appears that most people already have a congenital or general immunity to e.g. influenza and other viruses

This is confirmed by the findings on the cruise ship Diamond Princess, which was quarantined because of a few passengers who died of COVID-19

Most of the passengers were elderly and were in an ideal situation of transmission on the ship.

However, 75 % did not appear to be infected. So even in this high-risk group, the majority are resistant to the virus



Washington Post
10 June 2020

Are asymptomatic people spreading the coronavirus? A WHO official's words spark confusion, debate

William Wan and Miriam Berger

"We have a number of reports from countries who are doing very detailed contact tracing. They're following asymptomatic cases. They're following contacts. And they're not finding secondary transmission onward. It's very rare."

Maria Van Kerkhove, head of the WHO's emerging disease and zoonosis unit

“At this point, we simply don’t know how much asymptomatic transmission happens. Sometimes, it’s important to just say that.”

Eric Topol, a professor of molecular medicine at Scripps Research

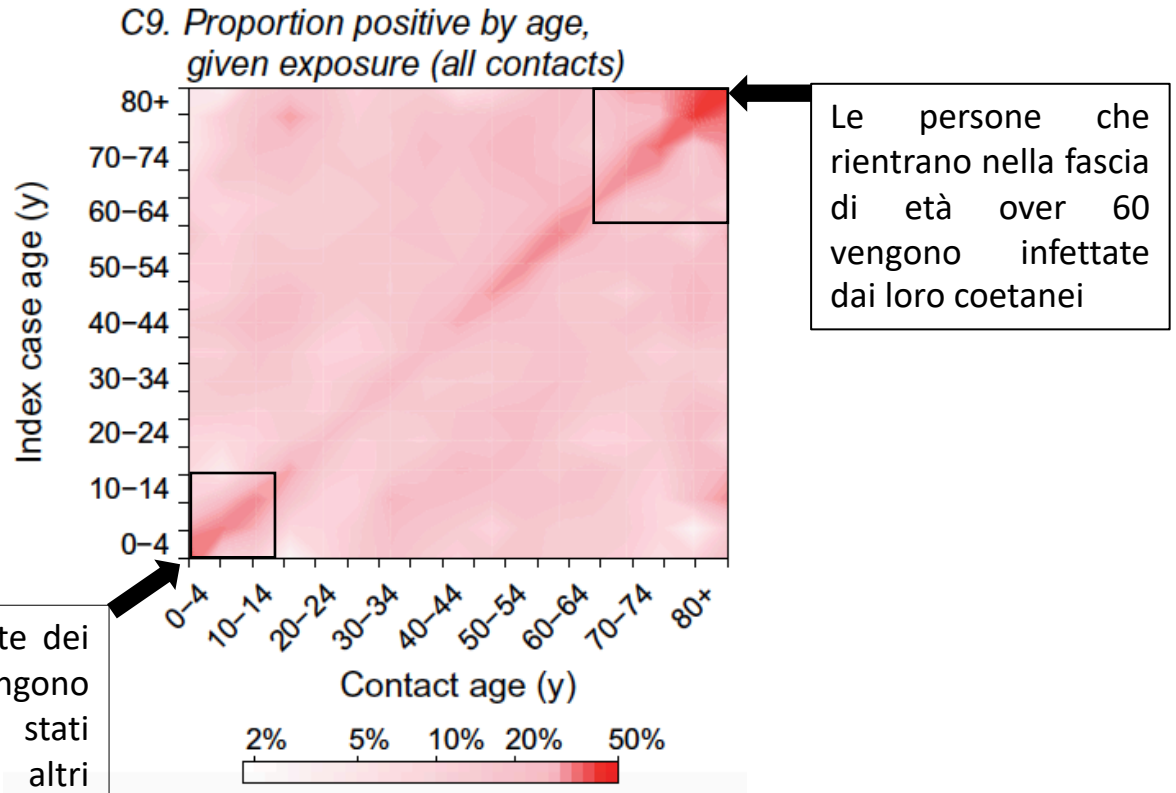
“At this point, we simply don’t know how much asymptomatic transmission happens. Sometimes, it’s important to just say that.”

Eric Topol, a professor of molecular medicine at Scripps Research

Il lavoro ha analizzato 84.965 infetti e ha monitorato i loro 575.071 contatti stretti.

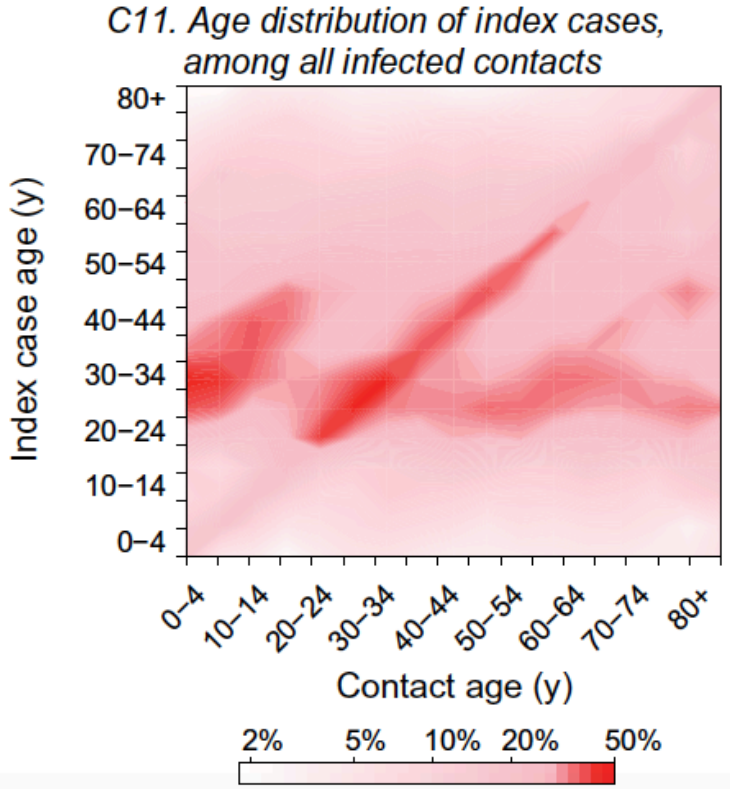
Hanno calcolato che il rischio di trasmissione da caso positivo a un contatto stretto era circa del 10%.

Andando ad analizzare per classi di età, hanno riscontrato che:



Le persone che rientrano nella fascia di età over 60 vengono infettate dai loro coetanei

La maggior parte dei bambini che vengono infettati sono stati contagiati da altri bambini



Esiste però una classe di età compresa tra i 20 e i 40 anni, che tende ad infettare tutte le fasce di età. Infatti, è responsabile del 50% delle infezioni riscontrate nei bambini, del 50% dei contagi dei propri coetanei e circa il 35% degli over 60.

Laxminarayan et al., Science 370, 691–697 (2020)

Nature | Vol 588 | 17 December 2020

HOW KIDS' IMMUNE SYSTEMS CAN EVADE COVID

By Bianca Nogrady

- I bambini si ammalano di rado di COVID-19 e il motivo potrebbe essere una risposta immunitaria molto diversa da quella degli adulti, così rapida ed efficace da eliminare il virus prima che si diffonda nell'organismo.

- Ciò sarebbe dovuto all'immaturità del sistema immunitario adattativo, a una forte risposta innata fin dalla nascita, o a una combinazione di fattori.

THE CLINICAL PRESENTATION OF COVID-19

- For about 80% of infected patients, COVID-19 is a mild disease that is mostly restricted to the upper and conducting airways, characterized by modest symptoms, similar to the common flu, including fever and a dry cough, which resolve spontaneously after 6 to 10 days

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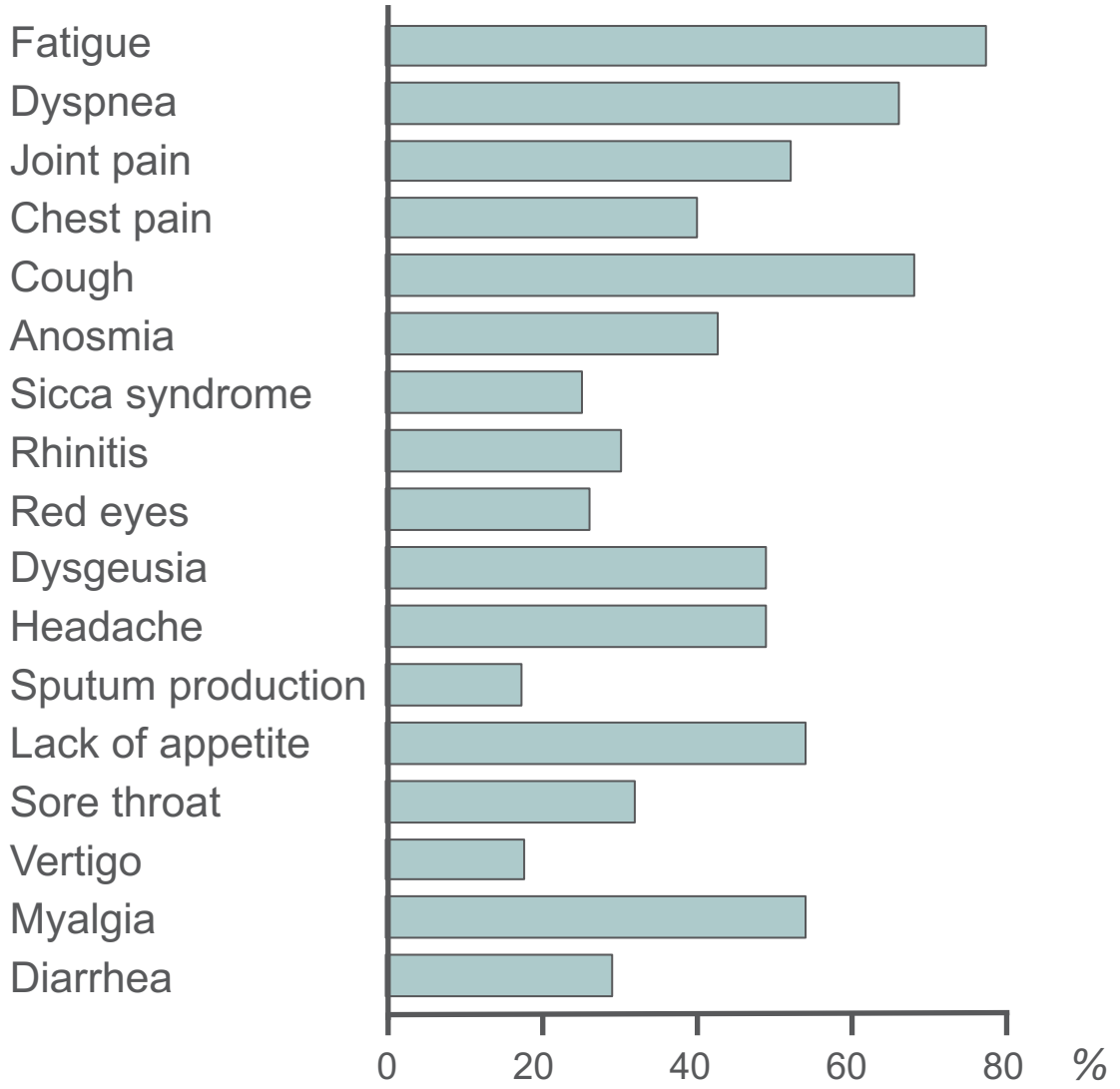
COMMON SYMPTOMS IN THE EARLY PHASE OF COVID-19



Carfì et al., *JAMA,* 2020

Clinical and Medical Investigations 2020

Review Article ISSN: 2398-5763

A recurrent question from a primary care physician: How should I treat my COVID-19 patients at home? An update

Fredy Suter[1#], Norberto Perico[2#], Monica Cortinovis[2] and Giuseppe Remuzzi[1,2*]

[1]Azienda Sociosanitaria Territoriale - Ospedale Papa Giovanni XXIII, Bergamo, Italy

[2]Istituto di Ricerche Farmacologiche Mario Negri, IRCCS, Bergamo, Italy

[#]Equally contributed

HOW CAN I TAKE CARE OF MY PATIENTS WITH INITIAL SYMPTOMS OF COVID-19 AT HOME?

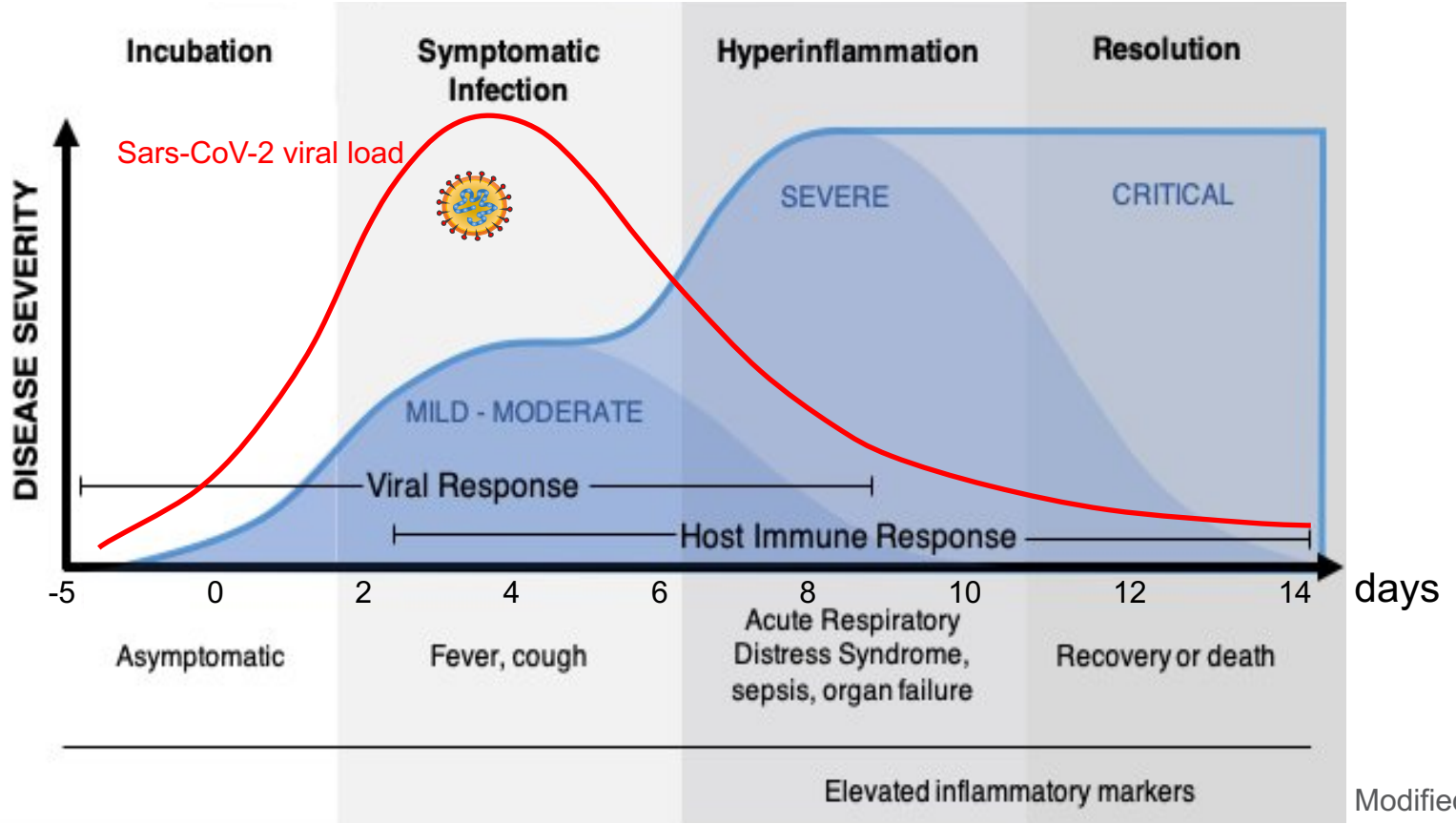
This is a recurrent question from primary care physicians, particularly in less fortunate parts of the world

- Do not expect to rely on results from controlled trials. If you are fortunate, it will take you 3 years to find an answer, which will then be contradicted by the next trial.
- By then, either the virus will have disappeared or a vaccine will have become available

Recommended treatments should start immediately when COVID-19 early symptoms appear without waiting results of a nasopharyngeal swab, if any

THE HOST IMMUNE RESPONSE LEADS TO EXACERBATION OF COVID-19

Accumulating evidence suggests that, host immune response, rather than the virus itself, underpins the progression of severe COVID-19 cases



Modified from Oberfeld et al., *Cell,* 2020

- Hyperinflammation response to SARS-CoV-2 contributes to disease severity and death in COVID-19
- Patients with severe COVID-19 have elevated clinical inflammatory markers and increased serum cytokine and chemokine levels
- These markers of inflammation are prognostic for the requirement of mechanical ventilation, the development of ARDS, and death in COVID-19

Gustine and Jones, *Am J Pathol,* 2021

Anti-inflammatory drugs

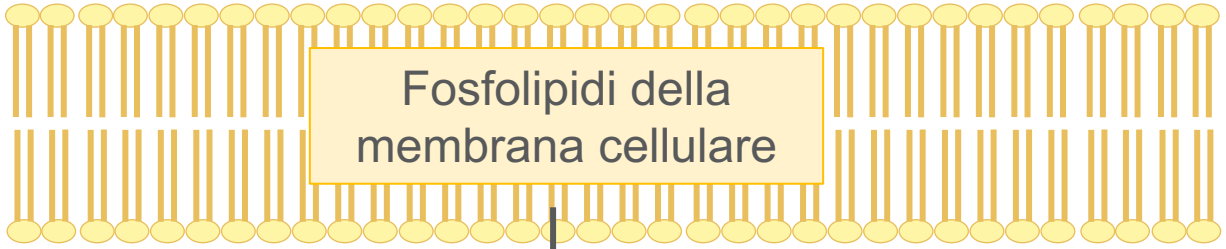
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Corticosteroids

Anticoagulants

- Low-molecular weight heparin

Other treatments

- Antibiotics
- Oxygen therapy



Acido arachidonico

Cicloossigenasi costitutiva

COX-1

Inibita da FANS*
Inibizione non desiderabile

Cicloossigenasi indotta durante l'infiammazione

COX-2

Inibita da COXIB
Inibizione desiderabile

Prostaglandine
Trombossani
Coinvolti nella omeostasi gastrointesinale, renale, piatrinica

Prostaglandine
Prostacicline
Mediatori dell'infiamnmazione

Gli inibitori selettivi della ciclossigenasi-2 (COX-2) mantengono l'effetto antinfiammatorio mediato dalle prostaglandine senza gli effetti negativi soprattutto a livello gastrico

* Farmaci Antiinfiammatori Non Steroidei

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

- Should the patient have myalgias/arthralgias or other painful symptoms, our advice is to administer a cyclooxygenase-2 (COX-2) inhibitor, including nimesulide and celecoxib.

- Nimesulide is readily available and at a high dose it maximally inhibits the COX-2 enzyme

Cullen et al., *J Pharm Exp Ther,* 1998

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

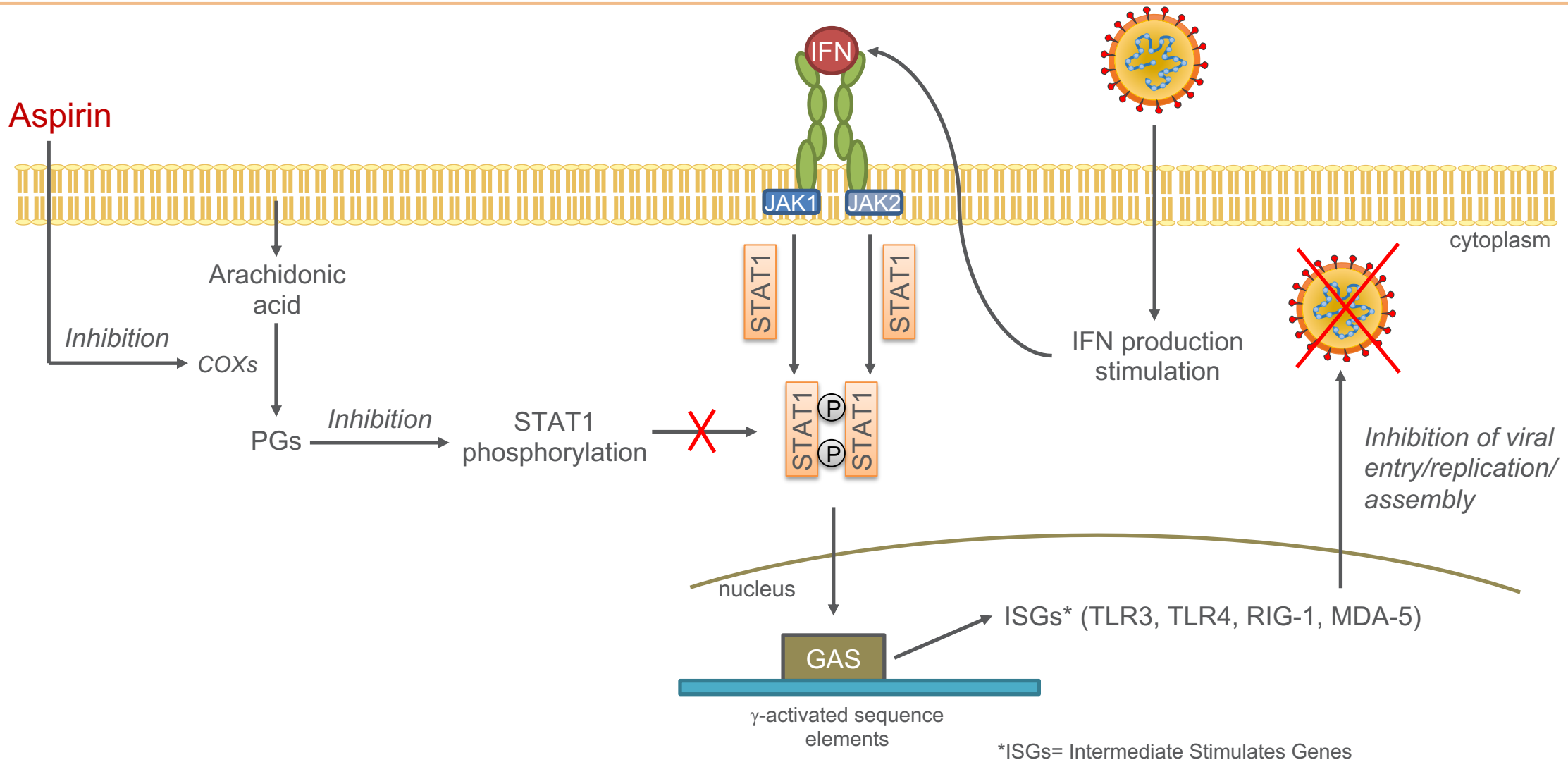
Nimesulide
100 mg b.i.d p.o, after a meal, for a maximum of 12 days

or

Celecoxib

First day:	- initial oral dose of 400 mg - a second dose of 200 mg
In the following days:	- up to maximum of 400 mg/day (200 mg twice a day), as needed

ANTI-VIRAL FUNCTION OF ASPIRIN



ANTI-VIRAL ACTIVITY OF ASPIRIN

- In vitro studies using virus-infected cell cultures aspirin showed a specific antiviral activity against influenza A, virus H1N1 and all human rhinoviruses

Glatthaar-Saalmuller et al., *Influenza and Other Respiratory Viruses,* 2017

- In a mouse-adapted model pharmacological inhibition of PGE_2 receptor EP2 and EP4 improved survival against lethal influenza A virus H1N1 infection, whereas PGE_2 administration reversed this phenotype

Coulombe et al., *Immunity,* 2014

ASPIRIN STIMULATES CELL-AUTONOMOUS IMMUNITY AGAINST VIRAL INFECTIONS

- Aspirin triggers the anti-inflammatory molecule resolvin D1 that in mice with herpes simplex virus (HSV-1) infection controls HSV-1-induced corneal lesions

  Rajasagi et al., *J Leuk Biol,* 2017

- In a cell culture system, acetylsalicylic acid inhibits hepatitis C virus replication in part through inhibition of COX-2 and activation of Mek1/2/p38 MAPK kinases

  Trujillo-Murillo et al., *Hepatology,* 2008

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Should the patient have fever (≥ 37.3 °C) or develop laboratory signs of hepatotoxicity associated with nimesulide or there are contraindications to celecoxib, these drugs should be substituted with aspirin (a COX-1 and COX-2 inhibitor)

Aspirin

- 500 mg twice a day p.o., after meal

Anesth Analg, 2020

Aspirin Use is Associated with Decreased Mechanical Ventilation, ICU Admission, and In-Hospital Mortality in Hospitalized Patients with COVID-19

Jonathan H Chow, et al.

- A retrospective, multicentre cohort study on 412 adult patients hospitalized with COVID-19, 98 of whom received low-dose aspirin within 24 hours of admission or 7 days prior to admission
- Aspirin use was independently associated with reduced risk of mechanical ventilation and intensive care unit admission

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

In patients with mild respiratory tract illness, anti-inflammatory therapies may prevent fatal cytokine storms induced by SARS-CoV-2 in the lung

COX2 INHIBITION IN THE TREATMENT OF COVID-19

Review of literature to propose repositioning of celecoxib for randomized controlled studies

- The concept of selective targeting COX2 and closely related cascades might be worth trying in the treatment pf COVID-19 given the substantial amount of data showing that COX2, p38 MAPK, IL1b, IL-6 and TGF-b play pivotal roles in coronavirus-related cell death, cytokine storm and pulmonary interstitial fibrosis

- Considering the lack of definitive treatment and importance of immunomodulation in COVID-19, COX2 inhibition might be a valuable adjunct to still-evolving treatment strategies

Baghaki et al., *Int J Infect Dis,* 2020

For treating COVID patients, these cardiovascular considerations might not be a major drawbacks since the expected duration of treatment with COX-2 inhibitors will not exceed a few days to weeks

Frontiers in Pharmacology, 2020

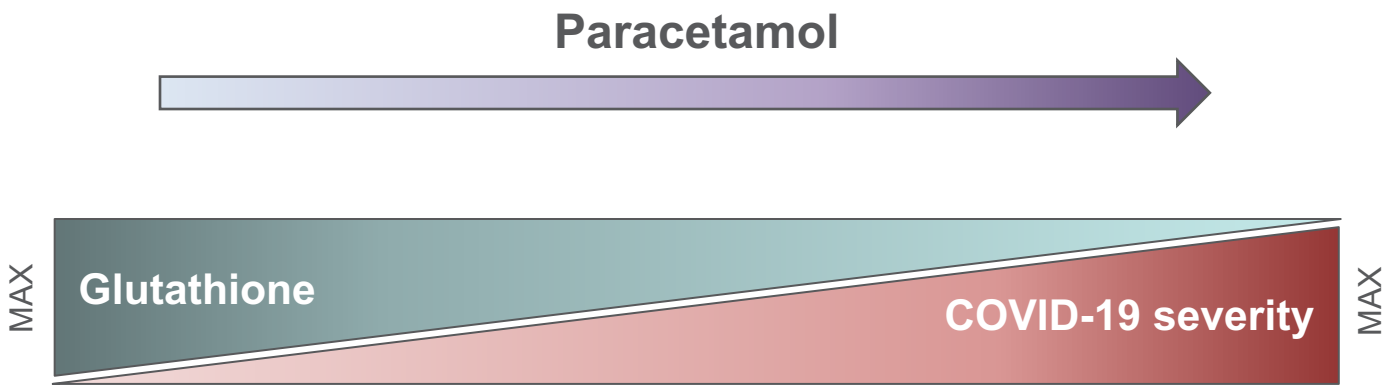
Paracetamol-Induced Glutathione Consumption: Is There a Link With Severe COVID-19 Illness?

Piero Sestili and Carmela Fimognari

- COVID-19 patients with low glutathione (GSH) levels and high radical oxygen species (ROS)/GSH ratio, experience the most severe illness

- The major risk factors for severe COVID-19 illness are aging, comorbidities, smoking habit, all characterized by intrinsically low antioxidant capacity and high ROS/GSH ratio

IN HEALTHY VOLUNTEERS, PARACETAMOL AND ITS METABOLITES DECREASE GSH LEVELS, ALSO WHEN GIVEN AT RELATIVELY LOW DOSES



Sestili and Fimognari, *Frontiers in Pharmacology*, 2020

After approximately 3 days from the onset of symptoms (or more days have elapses and the physician sees the patient for the first time)

Hematochemical tests

(blood cell count, D-dimer, CRP, creatinine, fasting blood glucose, ALT)

Should inflammatory indexes (CRP, neutrophil count, ALT, and D-dimer) be in the normal range, treatment with nimesulide/celecoxib (or aspirin) alone will continue

CORTICOSTEROIDS

Few days later

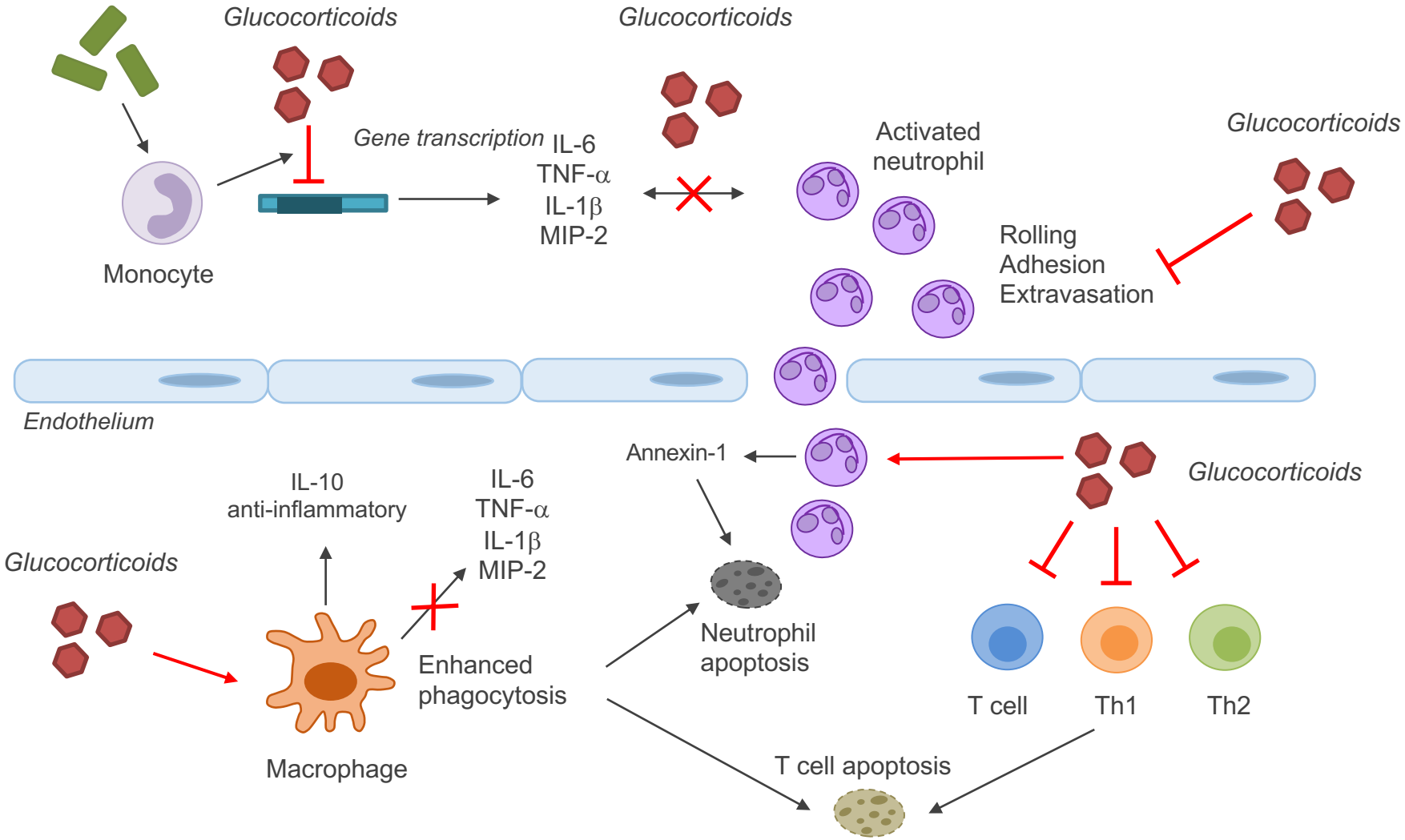
Repeat the hematochemical tests:

- mild increase in inflammatory indexes (CRP, neutrophil count)
  or
- persistent fever, myalgias, arthralgias, or other pain
  or
- cough or oxygen saturation (SpO_2) < 94-92 % occur

Thorax-Xray

Consider corticosteroids as add-on treatment at home (further decrease of the underlying inflammatory process)

CORTICOSTEROIDS



Cruz-Topete and Cidlowski, *NeuroImmunoModulation,* 2015

CORTICOSTEROIDS

Dexamethasone

- 8 mg p.o. for 3 days
- 4 mg p.o. for 3 further days
- 2 mg p.o. for 3 other days

42 mg dexamethasone total over 9 days

Duration of the corticosteroid treatment depends on the clinical evolution of the disease

CORTICOSTEROIDS

- During the early phase or in mild forms of COVID-19, when patients were not hospitalised, there appeared to be some evidence that corticosteroids may have been beneficial

  Russel et al., *Ecancermedscience,* 2020

- The initial lesions in the lungs of most of these patients may be minimal at chest radiography, but the lesions can spread to the entire lung fields within a day. Prompt intervention with corticosteroids can reverse or at least attenuate these initial events

  Lee et al., *Int J Mol Sci,* 2017

- Because the pathogenesis of pneumonia may be the same in all infected patients regardless of age, early control of immune/inflammatory-mediated lung injury can also be helpful in reducing morbidity and possibly mortality for these patients

  Lee et al., *Clin Exp Pediatr,* 2020
  Zhai et al., *Int J Antimicrob Agents,* 2020

ANTICOAGULANTS

- When the hematochemical tests (the first or the second set) show even a mild increase of D-dimer
- For bedridden patients even with mild symptoms

Anticoagulant prophylaxis with heparin

Low-molecule weight (LMW) heparin*

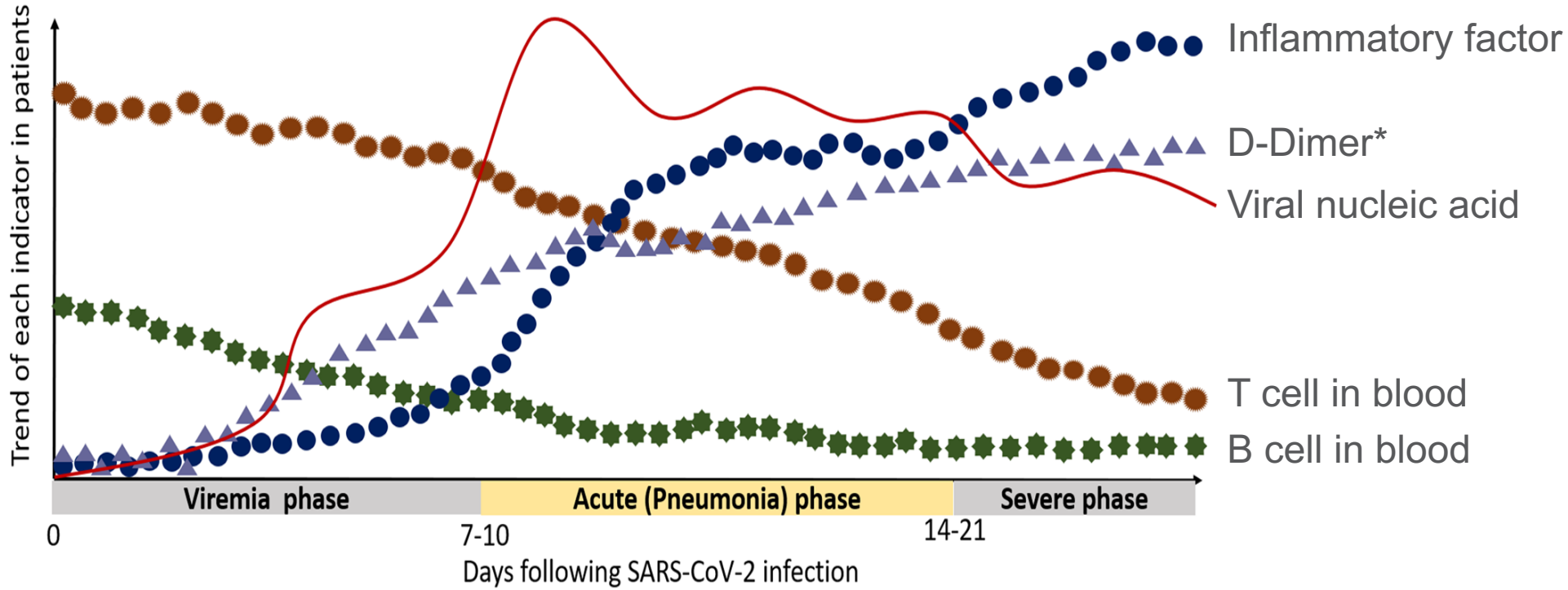
At the prophylactic daily dose of 4.000 U.I. subcutaneously

* unless contraindicated (e.g. ongoing bleeding or platelet count < 25 x 10^9/L

Treatment recommended for at least 7-14 days, independently of the patient recovering mobility

PROGRESSION OF SEVERE COVID-19 CASES

Among all the serum proteins, high levels of D-dimer have been identified as one of the most predictive marker for the poor prognosis of severe COVID-19



* D-dimer is a fibrin degradation product presents in the blood after fibrinolysis

Cao et al. *Cell Res.* 2020

ANTICOAGULANTS

Low-molecular weight heparin

- In non-hospitalised patients with mild COVID-19, the benefit of prophylactic administration of LMW heparin could extend beyond the prevention of thromboembolism in bedridden patients to control the possible initial activation of coagulation in the lung and other organs

- Moreover, the evidence that heparin may protect the endothelium and decrease the level of inflammatory biomarkers further supports the recommendation that COVID-9 patients be treated with this drug at home, as it can impact microcirculatory dysfunction and possibly limit organ damage

Liu et al., *J Surg Res,* 2019
Thachil, *J Thromb Haemost,* 2020

AGENZIA ITALIANA DEL FARMACO

Eparine a basso peso molecolare nei pazienti adulti con COVID-19

Ultima versione: 24/11/2020

Si forniscono di seguito elementi utile ad orientare la prescrizione e a definire un rapporto tra i benefici e i rischi sul singolo paziente	
Per quali pazienti sono raccomandabili?	**Uso a dosaggio profilattico** L'uso delle eparine a basso peso molecolare nella profilassi degli eventi tromboembolici nel paziente medico con infezione respiratoria acuta e allettato o con ridotta mobilità è raccomandato dalle principali linee guida in assenza di controindicazioni. Ciò si applica, in presenza delle caratteristiche suddette, sia a pazienti ricoverati, sia a pazienti gestiti a domicilio o nell'ambito di case di riposo o RSA

ANTICOAGULANTS

A recent retrospective study in 324 non-critically ill patients hospitalized with COVID-19 has shown that the rates of relevant bleeding events and mortality were higher in patients receiving (sub)therapeutic doses of heparin (as unfractionated LMW, or fondaparinux) than in those given prophylactic doses

Pesavento et al., *J Thromb Haemost,* 2020

OXYGEN THERAPY

- In the early phase of the disease before pulmonary symptoms manifest
- In the presence of progressively decreasing oxygen saturation (indicated by oximeter)*
- Following a first episode of dyspnea or wheezing

Gentle oxygen supply

* Suggested when SpO_2 < 94-92 %
  Required when SpO_2 < 90 %

at room air

CDC, April 2, 2020
Federazione Regionale degli Ordini dei Medici Chirurghi e degli Odontoiatri della Lombardia, Novembre 2020

OXYGEN THERAPY

With liquid O_2

- Start with 8-10 liter/min and monitor SpO_2 every 3-4 hours
- Titrate oxygen flow rate to reach target SpO_2 > 94 %
- Then, the rate of oxygen administration can be reduced to 4-5 liter/min (continue SpO_2 monitoring every 3-4 hours)

With gasous O_2

- Start with 2.5-3.0 liter/min, but monitor SpO_2 more frequently than with liquid oxygen
- Titrate flow rates to reach target SpO_2 > 94 %

* Should patients be poorly responsive to high O_2 administration, consider hospitalization, if feasible

OTHER TREATMENTS

Antibiotics

Antibiotics are not mandatory, but sometimes necessary in COVID-19 patients

- with bacterial pneumonia or suspected secondary bacterial upper respiratory tract infections
- particularly fragile patients
- when hematochemical inflammation indexes (CRP, neutrophil count) are markedly altered

ANTIBIOTICS

Azithromycin

- 500 mg/day p.o. for 6 days

or

Cefixime*

- 400 mg/day p.o. for 6 days

* as alternative to azithromycin should the patient be a risk of or with a history of cardiac arrhythmia

ANTIBIOTICS

Many COVID-19 patients die of secondary bacterial infections rather than of the SARS-CoV-2 viral infection itself

- In a Chinese cohort of 247 hospitalized COVID-19 patients, 15 % acquired bacterial infections - of these, 50 % died

Zhou et al., *Lancet,* 2020

- Secondary bacterial pneumonia was the major cause of death during other major respiratory viral outbreaks (e.g. 150 out 300 thousand people during the 2009 H1N1 infection, and the majority of people during the 1918 Spanish flu)

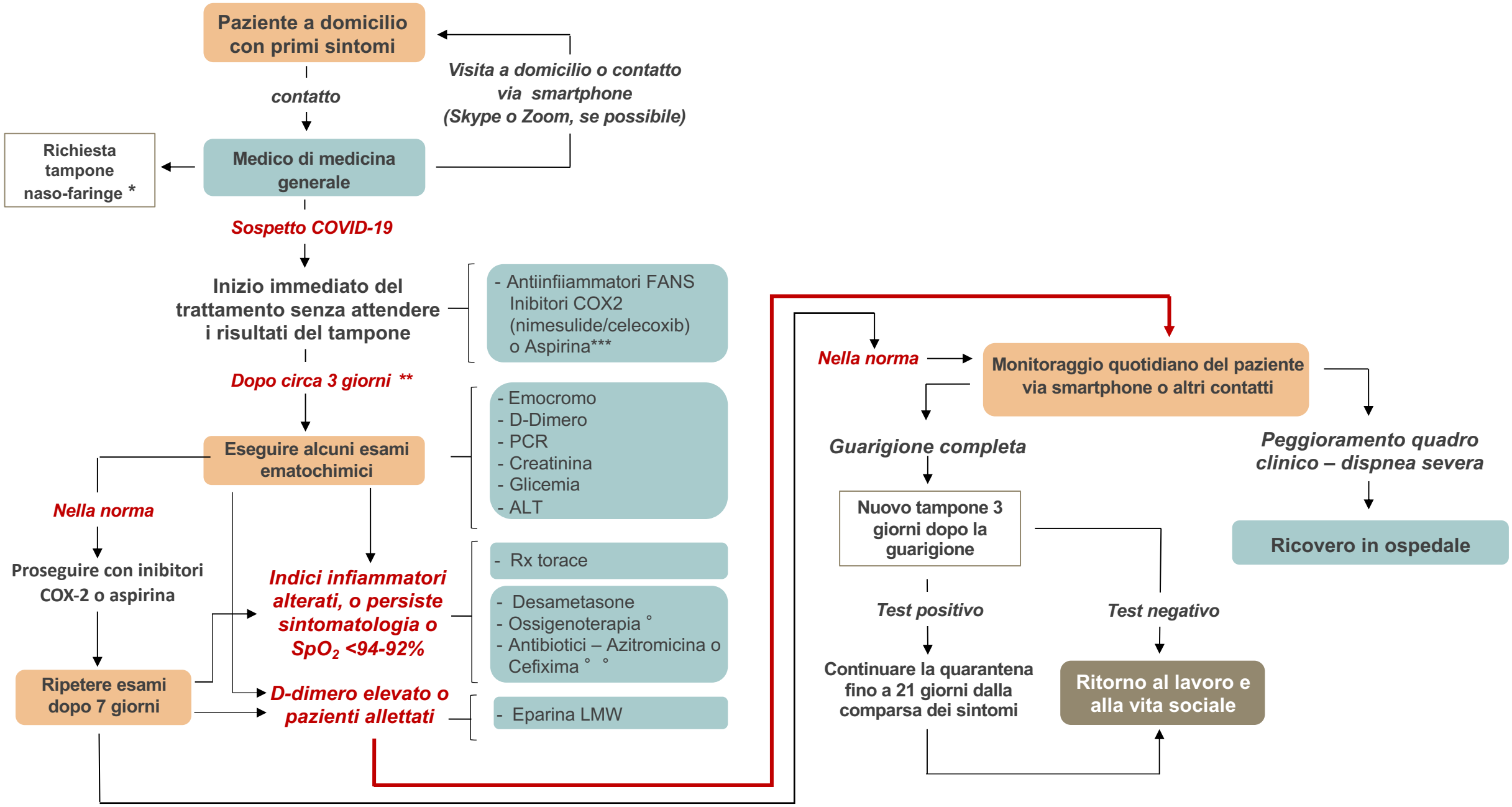
THE USE OF AZITHROMYCIN

- It has raised some concerns because this drug, as it occurs with macrolides, can block ion channels and may affect the cardiac electrical pattern

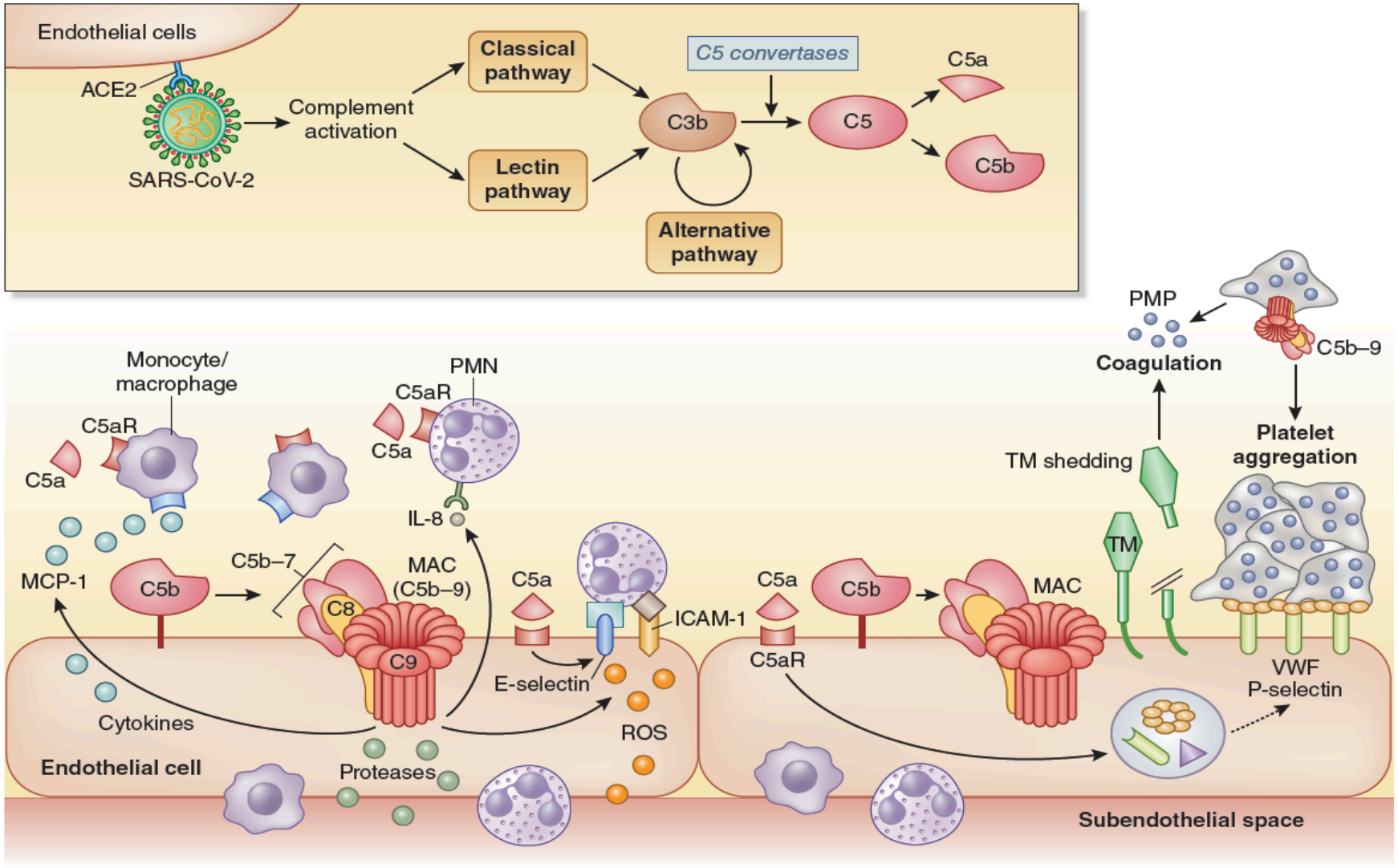
  Lu et al., *Expert Opin Drug Saf,* 2015

- In a Cochrane review of adverse events in people taking macrolide antibiotics for any indications, the use of these drugs, including azithromycin, was not associated with a higher risk of cardiac disorders compared to placebo

  Hansen et al., *Cochrane Database Syst Rev,* 2019


Paziente a domicilio con primi sintomi
Visita a domicilio o contatto via smartphone (Skype o Zoom, se possibile)
contatto
Richiesta tampone naso-faringe *
Medico di medicina generale
Sospetto COVID-19
Inizio immediato del trattamento senza attendere i risultati del tampone
- Antiinfiammatori FANS Inibitori COX2 (nimesulide/celecoxib) o Aspirina***
Dopo circa 3 giorni **
Eseguire alcuni esami ematochimici
- Emocromo
- D-Dimero
- PCR
- Creatinina
- Glicemia
- ALT
Nella norma
Proseguire con inibitori COX-2 o aspirina
Indici infiammatori alterati, o persiste sintomatologia o SpO2 <94-92%
- Rx torace
- Desametasone
- Ossigenoterapia °
- Antibiotici – Azitromicina o Cefixima ° °
Ripetere esami dopo 7 giorni
D-dimero elevato o pazienti allettati
- Eparina LMW
Nella norma
Monitoraggio quotidiano del paziente via smartphone o altri contatti
Guarigione completa
Peggioramento quadro clinico – dispnea severa
Ricovero in ospedale
Nuovo tampone 3 giorni dopo la guarigione
Test positivo
Test negativo
Continuare la quarantena fino a 21 giorni dalla comparsa dei sintomi
Ritorno al lavoro e alla vita sociale

COMPLEMENT-INDUCED COAGULOPATHY UNDERPINS THE SYSTEMIC MULTIORGAN MICROANGIOPATHY OBSERVED IN SEVERE COVID-19 CASES



Noris et al., *Kidney Int,* 2020

A VACCINE THAT STOPS COVID-19 WON'T BE ENOUGH

- A vaccine is never 100 percent effective, 100 percent safe and available to 100 percent of people
- We're not going to get a vaccine to 7 billion people on the planet, and 7 billion people on the planet aren't going to want to take it
- I'm pretty sure we're going to have a vaccine next year, but that isn't going to mean we're going to be able to go back to our fully normal lives

COVID-19 VACCINES NO TIME FOR COMPLACENCY

- Can infection provide sterilising immunity?
- How quickly does protective immunity wane?
- How severe might reinfection be?
- How does immunity vary by sex, ethnicity, and age?
- Will we have annual seasonal outbreaks?
- Or longer spells of quiescence punctuated by re-emergence?
- And how will health systems have to adapt accordingly?

These issues and many others will determine the continuing impacts of COVID-19 on health and all are still poorly understood

Editorial, *Lancet,* November 21, 2020

Science, 11 September 2020

An ethical framework for global vaccine allocation

The Fair Priority Model offers a practical way to fulfill pledges to distribute vaccines fairly and equitably

Emanuel et al.,

Vaccine allocation among countries raises complex and controversial issues involving public opinion, diplomacy, economics, public health, and other considerations.

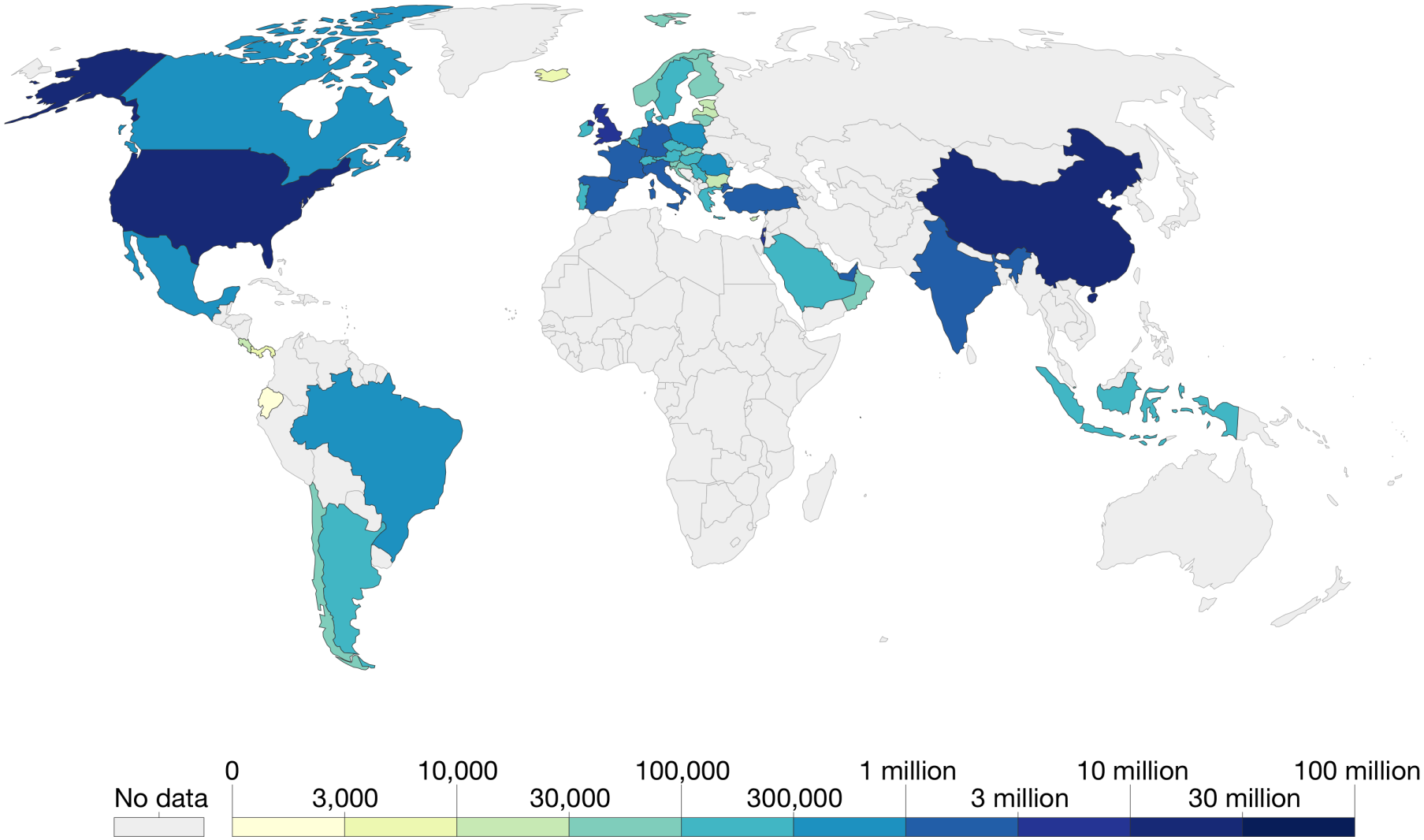
Yet little progress has been made toward delineating what constitutes fair international distribution of vaccine

Many have endorsed "equitable distribution of COVID-19…vaccine" without describing a framework or recommendations

COVID-19 vaccine doses administered, Jan 24, 2021

Total number of vaccination doses administered. This is counted as a single dose, and may not equal the total number of people vaccinated, depending on the specific dose regime (e.g. people receive multiple doses).

Our World in Data



THE FAIR PRIORITY MODEL IS PRIMARILY ADDRESSED TO THREE GROUPS

COVAX facility—led by Gavi, the WHO, and the Coalition for Epidemic Preparedness Innovations (CEPI)— which intends to purchase vaccines for fair distribution across countries

Vaccine producers. Thankfully, many producers have publicly committed to a “broad and equitable” international distribution of vaccine

National governments, some of whom have also publicly committed to a fair distribution

These groups need a clear framework

Emanuel et al., *Science,* 2020

FAIRLY DISTRIBUTING A COVID-19 VACCINE AMONG COUNTRIES IS A PROBLEM OF DISTRIBUTIVE JUSTICE

Although governments will be the initial recipients of vaccine, fair distribution across countries must reflect a moral concern for the ultimate recipients: individuals

Three values are particularly relevant:

- benefiting people and limiting harm
- prioritizing the disadvantaged
- equal moral concern

Emanuel et al., *Science,* 2020

A heated debate has taken place over how to distribute the COVID-19 vaccines

For those that require two shots, should the period between them be stretched so that more people can be vaccinated sooner?

Should the second shot be dropped altogether?

Should a half-dose of each shot be given to younger folks at less risk for infection?

Outstanding scholars have taken different positions on this, and the United Kingdom decided to stretch the interval between doses substantially

Thorp, Science, 2021

The debate led to what seems like a good outcome in the United States: the FDA decided not to deviate from the protocols followed followed in the phase 3 clinical trials. That makes sense.

Right now, the main constraint for mass vaccination lies in the logistics for administering the shots themselves, not in having a sufficient supply of vaccine

The Biden transition team just announced a plan to get more people vaccinated while working to ensure that enough vaccine will be in place for the second shots

Thorp, Science, 2021

Corriere della Sera, 21 gennaio 2021

Le seconde iniezioni posticipate per immunizzare più persone
Ecco perché la scelta dell'Inghilterra è una strada possibile

I VANTAGGI DI RINVIARE IL RICHIAMO

Il dibattito

di **Giuseppe Remuzzi**

EDITORIAL

Public debate is good for science

In the age of the internet, there's no such thing as a private debate. But is that bad for science? Some scientists have had misgivings. When debates in any sector move beyond the halls of universities and government agencies, there is potential for misuse of information and public confusion. But open debate can also foster communication among scientists and between the scientific community and the public. During the pandemic, open debate on research, health, and policy—whether on television, in newspapers, or on social media—widened public attention and encouraged more diverse voices. If this trend spurs scientists to agree more quickly about the best solutions to our problems—and at the same time helps the public "see" the process of scientific discourse more clearly—then this is good for everyone, including scientists.

I pay attention to scientists' public conversations about COVID-19—including the fast-paced exchanges on Twitter—because my role in communicating science includes amplifying consensus while steering clear of becoming an armchair epidemiologist or immunologist. For most of the pandemic, the trusted experts have generally agreed on issues like social distancing and a rigorous analysis of clinical trial data by the U.S. Food and Drug Administration (FDA) and other agencies. But there have been areas where a consensus has not emerged, such as whether and when to close schools or the usefulness of masks.

More recently, a heated debate has taken place over how to distribute the COVID-19 vaccines. For those that require two shots, should the period between them be stretched so that more people can be vaccinated sooner? Should the second shot be dropped altogether? Should a half-dose of each shot be given to younger folks at less risk for infection? Outstanding scholars have taken different positions on this, and the United Kingdom decided to stretch the interval between doses substantially. The debate led to what seems like a good outcome in the United States: The FDA decided not to deviate from the protocols followed in the phase 3 clinical trials. That makes sense. Right now, the main constraint for mass vaccination lies in the logistics for administering the shots themselves, not in having a sufficient supply of vaccine. The Biden transition team just announced a plan to get more people vaccinated while working to ensure that enough vaccine will be in place for the second shots.

Although this seems like a sound decision, some have questioned the manner in which the debate was conducted. When epidemiologist Michael Mina and sociologist Zeynep Tufekci considered the issue in an op-ed in *The New York Times*, some scientific experts worried that such public speculation might create confusion or lead people to believe that disagreement over the details meant a lack of adequate scientific consensus over the safety and efficacy of the vaccines. Should such discussions take place only in scientific journals? Or only informally on Twitter?

The anxiety seems misplaced. The days of going to a Gordon Conference or Asilomar and having a confidential debate about scientific issues are gone, and that's for the best beca
were not div
cluded a lot
These days, t
debates about science regardless
place, so the medium isn't so
What matters is getting to the ri
the science—deciding what the
the appropriate way of answerin
interpretation of the data. For m
debate is a new frontier and it n
West (it may well be). But rathe
conversations, let the debates be
orous, wherever they are held. I
to understand that science is ar
recting process, let's do away onc
idea that science is a fixed set o
Instead, let everyone see the noisy
that advance science and lead to
us all.

–H. Holden Thorp

> "...let the debates be transparent and vigorous, wherever they are held."

H. Holden Thorp
Editor-in-Chief,
Science journals.
hthorp@aaas.org
@hholdenthorp

If we want the public to understand that science is an honorably self-correcting process, let's do away once and for all with the idea that science is a fixed set of facts in a textbook. Instead, let everyone see the noisy, messy deliberations that advance science and lead to decisions that benefit us all.

COVID-19 WILL CHANGE OUR MIND

- The concept of One Health will become a new priority
- My health depends on your health. Your health depends on my health
- We cannot escape one other
- The liberties that we prize so highly depend on the health of all of us
- We cannot say that politics and priorities of my country are of no concern to you. Just as the politics and priorities of your country are a legitimate interest of mine
- Sovereignty is dead

These slides belong to
Giuseppe Remuzzi, *M.D.*
Mario Negri Institute for
Pharmacological Research,
Bergamo, Italy

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