SARS-CoV-2 – izazov za klasičnu i molekularnu medicinu

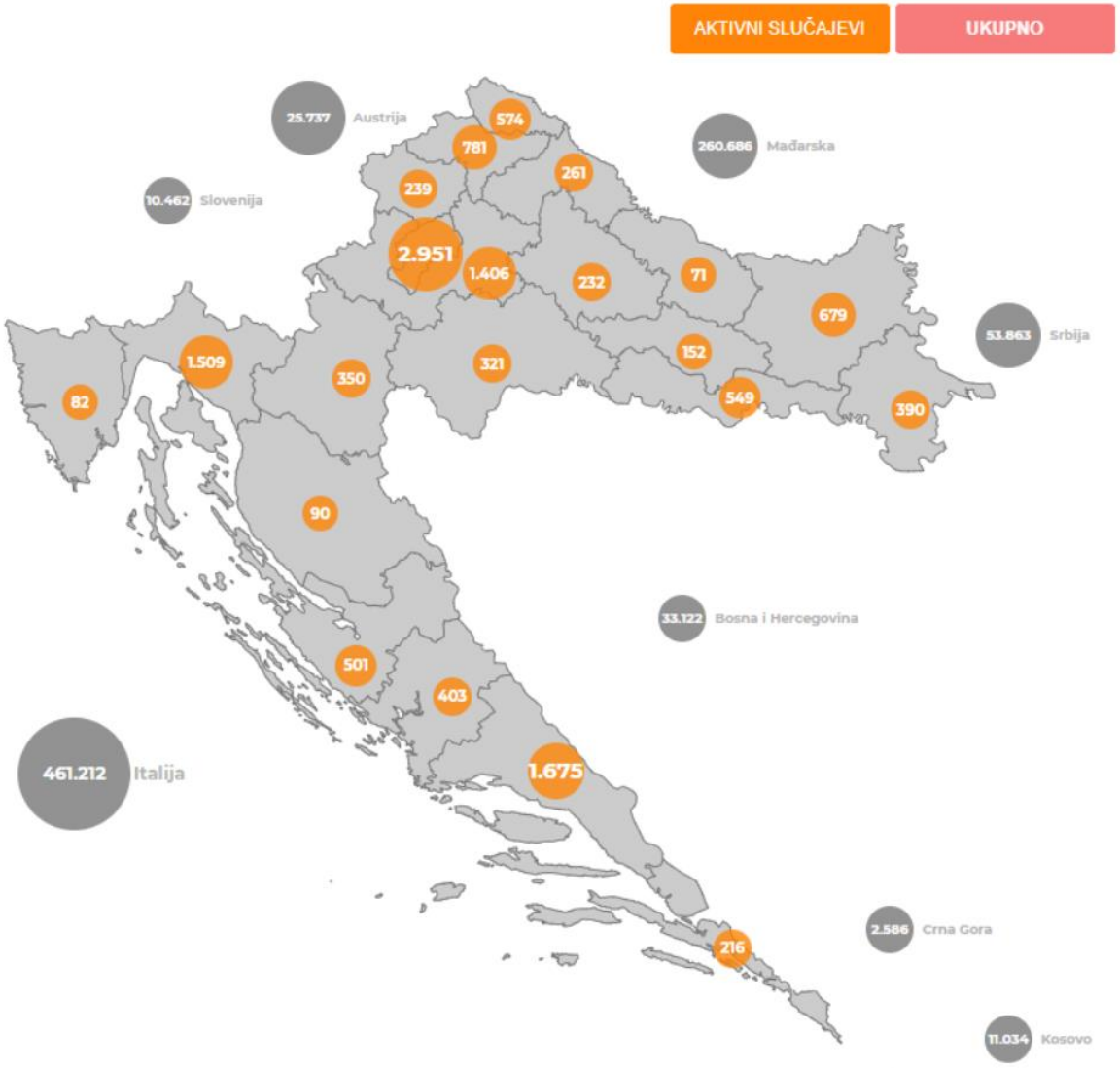
Prof.dr.sc. Alemka Markotić
Klinika za infektivne bolesti „Dr. Fran Mihaljević“

Ažurirano 26.04. u 11:11

Izvor: Hrvatski zavod za javno zdravstvo

SLUČAJEVI	OPORAVLJENI	PREMINULI
HR: **323.036**	HR: **302.699**	HR: **6.905**
Svijet: **147.809.201**	Svijet: **125.360.149**	Svijet: **3.122.922**

Koronavirus – statistički pokazatelji za Hrvatsku i EU



410 novih slučajeva u protekla 24 sata, u bolnicama ukupno 2.315 osoba

U protekla 24 sata zabilježeno je 410 novih slučajeva pa je broj aktivnih slučajeva u Hrvatskoj danas ukupno 13.432. Među njima je 2.315 pacijenata na bolničkom liječenju, od toga je na respiratoru 259 pacijenata. U protekla 24 sata oporavilo se 2.207 osoba, a testirano je njih 3.417.

26.04.2021. 11:10

Željko Cvetnić

Bolesti koje su mijenjale svijet

MEDICINSKA NAKLADA
HRVATSKI VETERINARSKI INSTITUT

Symposium "New Coronavirus from China: Biosecurity Threat and Challenge for Healthcare Professionals"

Authors:
Alemka Markotić
Ljiljana Žmak
Rok Civljak
Ivan Christian Kurolt
Vida Demarin

The symposium "New Coronavirus from China: Biosecurity Threat and Challenge for Health Care Professionals" was held at the Croatian Academy of Sciences and Arts, on February 14, 2020. In late 2019, a severe respiratory infection caused by SARS-CoV-2 started to spread rapidly, resulting in high morbidity and mortality rates in Wuhan, China, and continued to spread even faster worldwide, causing immeasurable health and economic challenges.

The goal of this symposium, organized by the Croatian Society for Biosafety and Biosecurity in cooperation with the Croatian Academy of Sciences and Arts and the University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb, was to gather a large number of experts in the field of biosafety, infectious diseases, microbiology, epidemiology, molecular biology, as well as other health experts to discuss current possibilities in the treatment, diagnosis and prevention of the Coronavirus disease 2019 (COVID-19).

Due to the exceptional interest in the symposium, it was organised simultaneously in the large hall of the Croatian Academy of Sciences and Arts and the Library of the Croatian Academy of Sciences and Arts, which were linked by a video link. However, the interest in the symposium exceeded the capacity of these two conference rooms, thus the entire symposium was broadcasted live on YouTube. The symposium was also recorded, which enabled future watching both on YouTube and on the websites of the Croatian Society for Biosafety and Biosecurity, the Croatian Academy of Sciences and Arts and the University Hospital for Infectious Diseases "Dr. Fran Mihaljević".

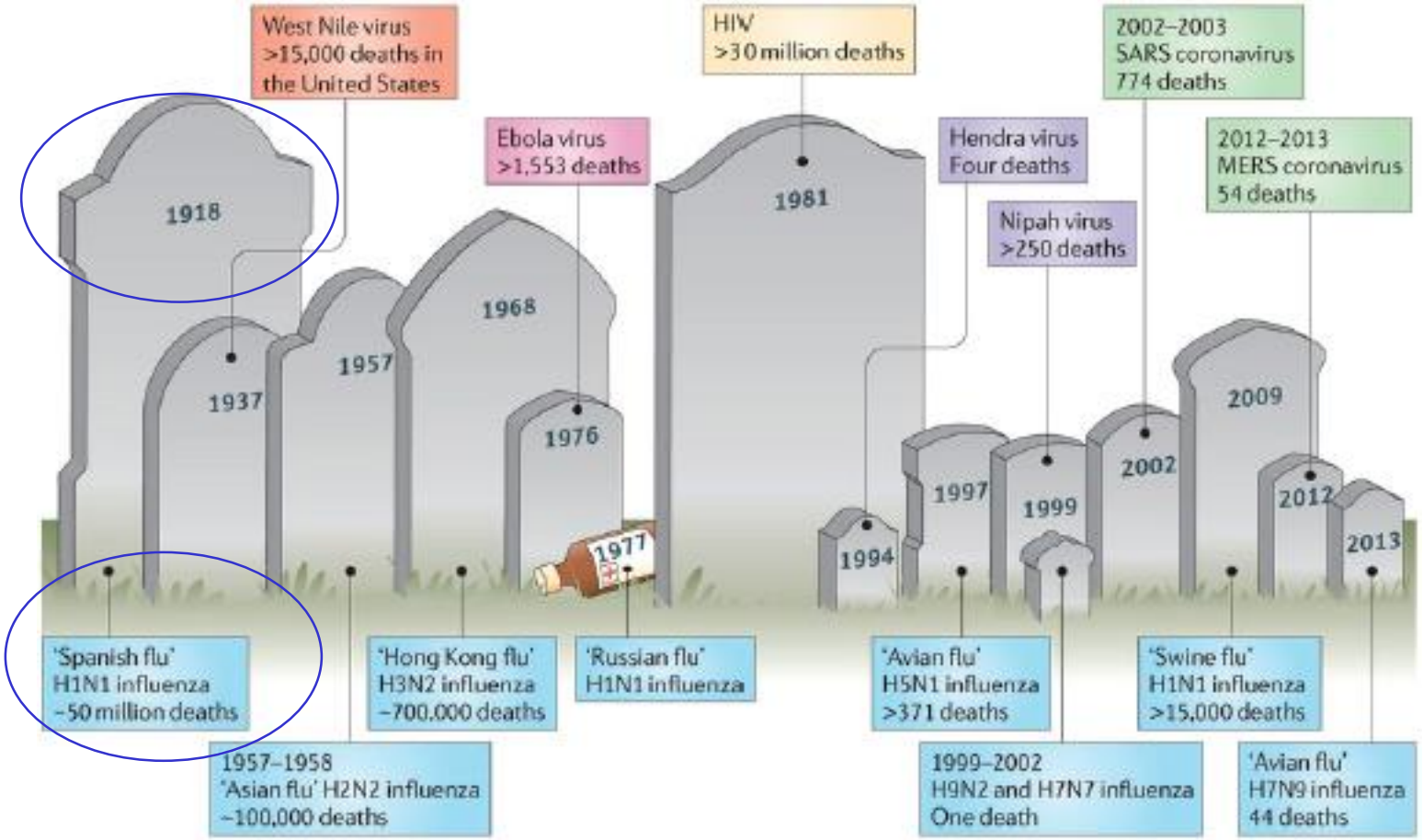
Speeches at the symposium were held by leading exprets in the field. First, the director of the University Hospital for Infectious Diseases "Dr. Fran Mihaljević ", professor Alemka Markotić reminded the participants of the causes and consequences of previous dangerous infectious diseases epidemics and pandemics, from plague in the Middle Ages to Ebola in the 21th century. Academician Josip Madić spoke about coronaviruses in veterinary medicine, while professor Antoinette Kaić Rak, Head of the World Health Organization Office in the Republic of Croatia, spoke about the new coronavirus as a global threat.

The Minister of Health, Vili Beroš, was also a speaker at the symposium, reporting on the results of the meeting of the Ministers of Health of the European Union countries held on February 13 in Brussels. Professor Beroš convened the meeting as minister of health, as Croatia is currently holding the presidency of the Council of the European Union. The main goal of the meeting was to ensure better coordination of measures to combat the threat of coronavirus spread. The meeting pointed out possible issues in the procurement of medicines and medical equipment from China. Minister Beroš expressed satisfaction that such a meeting was organized in a short time, emphasizing that it is a success of Croatian diplomacy.

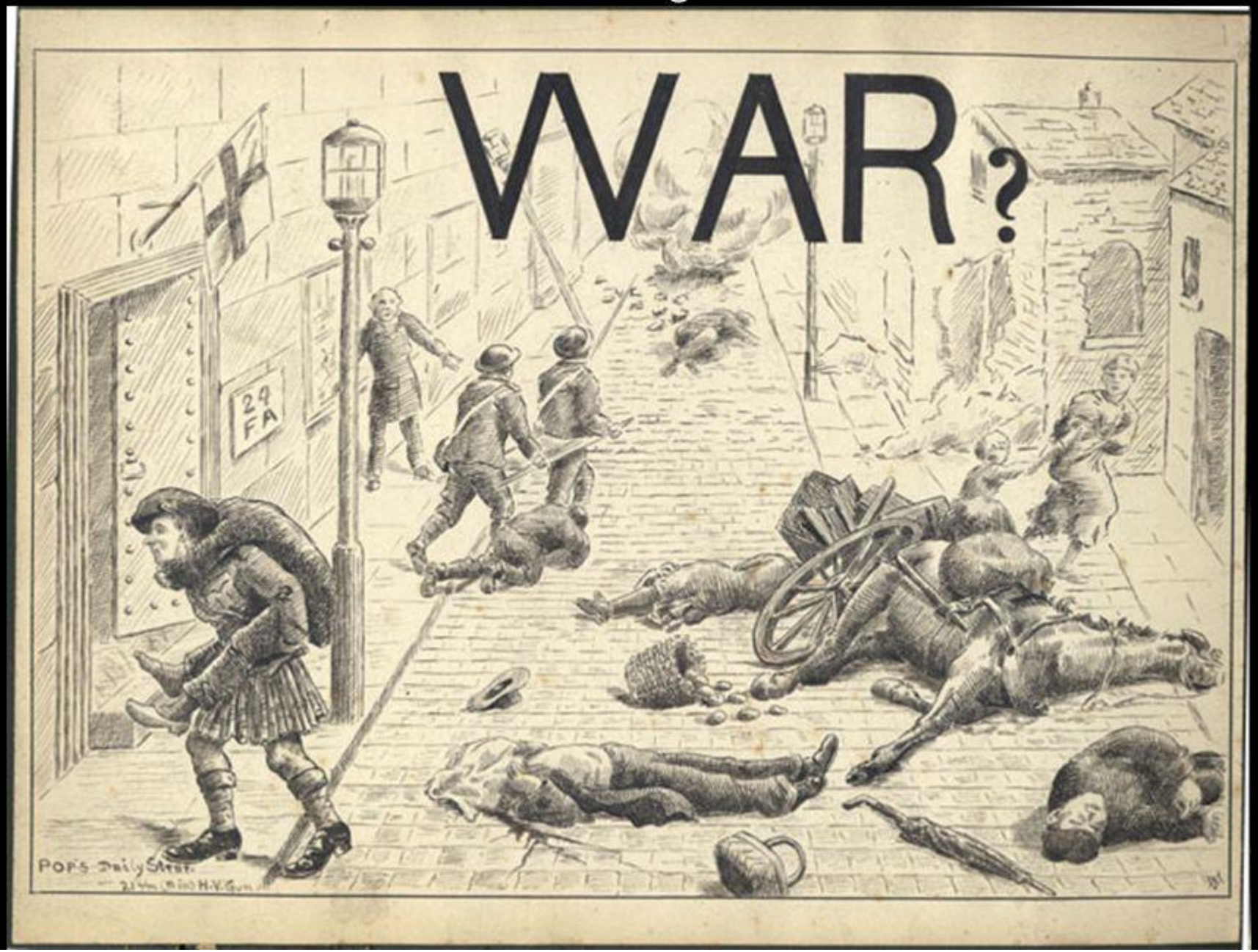
Bernard Kaić, MD, PhD, Head of the Infectious Diseases Epidemiology Service at the Croatian Institute of Public Health presented the epidemiological features of the recent coronaviruses causing-severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the new coronavirus, SARS-CoV-2. The clinical features of the COVID-19 were described by assistant professor Rok Čivljak, Deputy Director of the University Hospital for Infectious Diseases "Dr. Fran Mihaljević". Assistant professor Marko Kutleša, Head of the Department of Intensive Care Medicine and Neuroinfectology, at the University Hospital for Infectious Diseases "Dr. Fran Mihaljević" covered the treatment of patients with severe respiratory infections admitted in the intensive care unit. Ivan Christian Kurolt, PhD from the University Hospital for Infectious Diseases "Dr. Fran Mihaljević", who established positive reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) nucleic acid test for SARS CoV-2 in late January, and head of the Biosafety Level-3 (BSL-3) laboratory gave a speech about the molecular diagnosis of the new coronaviruseDr. Kurolt.

The first case of COVID-19 in Croatia was confirmed on February 25. Over the next two weeks, sporadic COVID-19 cases were reported, after which the number of new cases recorded per day gradually increased. Measures taken to limit and prevent the spread of SARS-CoV-2, prompt diagnosis and treatment of COVID-19 patients, have ranked Croatia among the world's top countries that have so far successfully fought this dangerous pandemic.

Emergentni patogeni – nevidljivi ubojice



WWI killed 10 million in battle
2 million died of hunger related to war



Etiologija

即时 ...准与消费支出挂钩比例 ▪ 消费提示：直播购物成为新型投诉热点 ▪ 浙江成立人才小贷公... 客户端 搜索 频道 下一篇 春运大幕明将开启 回家路上新...

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专家称系新型冠状病毒 武汉不明原因的病毒性肺炎疫情病原学鉴定取得初步进展

2020-01-09 09:45:59 来源：新华网

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新华社北京1月9日电（记者屈婷）日前，就武汉不明原因的病毒性肺炎疫情病原学鉴定进展问题，记者采访了病原检测结果初步评估专家组组长、中国工程院院士徐建国。他表示，专家组认为，本次不明原因的病毒性肺炎病例的病原体初步判定为新型冠状病毒。

问题一：目前，武汉不明原因的病毒性肺炎疫情病原学鉴定有什么进展？

徐建国：截至2020年1月7日21时，实验室检出一种新型冠状病毒，获得该病毒的全基因组序列，经核酸检测方法共检出新型冠状病毒阳性结果15例，从1例阳性病人样本中分离出该病毒，电镜下呈现典型的冠状病毒形态。

On 31 December 2019, the Wuhan Municipal Health Commission in Wuhan City, Hubei province, China, reported a cluster of pneumonia cases (including seven severe cases) of unknown aetiology, with a common reported link to Wuhan's Huanan Seafood Wholesale Market, a wholesale fish and live animal market.

On 9 January 2020, China's CDC reported that a novel coronavirus (later named SARS-CoV-2, the virus causing COVID-19) had been detected as the causative agent for 15 of the 59 cases of pneumonia

Novel 2019 coronavirus genome

SARS-CoV-2 coronavirus

edward_holmes 6 Jan '20

> 10th January 2020
> This posting is communicated by Edward C. Holmes, University of Sydney on behalf of the consortium led by Professor Yong-Zhen Zhang, Fudan University, Shanghai

The Shanghai Public Health Clinical Center & School of Public Health, in collaboration with the Central Hospital of Wuhan, Huazhong University of Science and Technology, the Wuhan Center for Disease Control and Prevention, the National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control, and the University of Sydney, Sydney, Australia is releasing a coronavirus genome from a case of a respiratory disease from the Wuhan outbreak. The sequence has also been deposited on GenBank (accession MN908947 30.0k) and will be released as soon as possible.

Update: This genome is now available on GenBank and an updated version has been posted 30.0k.

Disclaimer:
Please feel free to download, share, use, and analyze this data. We ask that you communicate with us if you wish to publish results that use these data in a journal. If you have any other questions –then please also contact us directly.

Professor Yong-Zhen Zhang,
Shanghai Public Health Clinical Center & School of Public Health,
Fudan University,
Shanghai, China.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

N ENGL J MED 382;8 NEJM.ORG FEBRUARY 20, 2020

A Novel Coronavirus from Patients with Pneumonia in China, 2019

Na Zhu, Ph.D., Dingyu Zhang, M.D., Wenling Wang, Ph.D., Xingwang Li, M.D., Bo Yang, M.S., Jingdong Song, Ph.D., Xiang Zhao, Ph.D., Baoying Huang, Ph.D., Weifeng Shi, Ph.D., Roujian Lu, M.D., Peihua Niu, Ph.D., Faxian Zhan, Ph.D., Xuejun Ma, Ph.D., Dayan Wang, Ph.D., Wenbo Xu, M.D., Guizhen Wu, M.D., George F. Gao, D.Phil., and Wenjie Tan, M.D., Ph.D., for the China Novel Coronavirus Investigating and Research Team

SUMMARY

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China. A previously unknown betacoronavirus was discovered through the use of unbiased sequencing in samples from patients with pneumonia. Human airway epithelial cells were used to isolate a novel coronavirus, named 2019-nCoV, which formed a clade within the subgenus sarbecovirus, Orthocoronavirinae subfamily. Different from both MERS-CoV and SARS-CoV, 2019-nCoV is the seventh member of the family of coronaviruses that infect humans. Enhanced surveillance and further investigation are ongoing. (Funded by the National Key Research and Development Program of China and the National Major Project for Control and Prevention of Infectious Disease in China.)

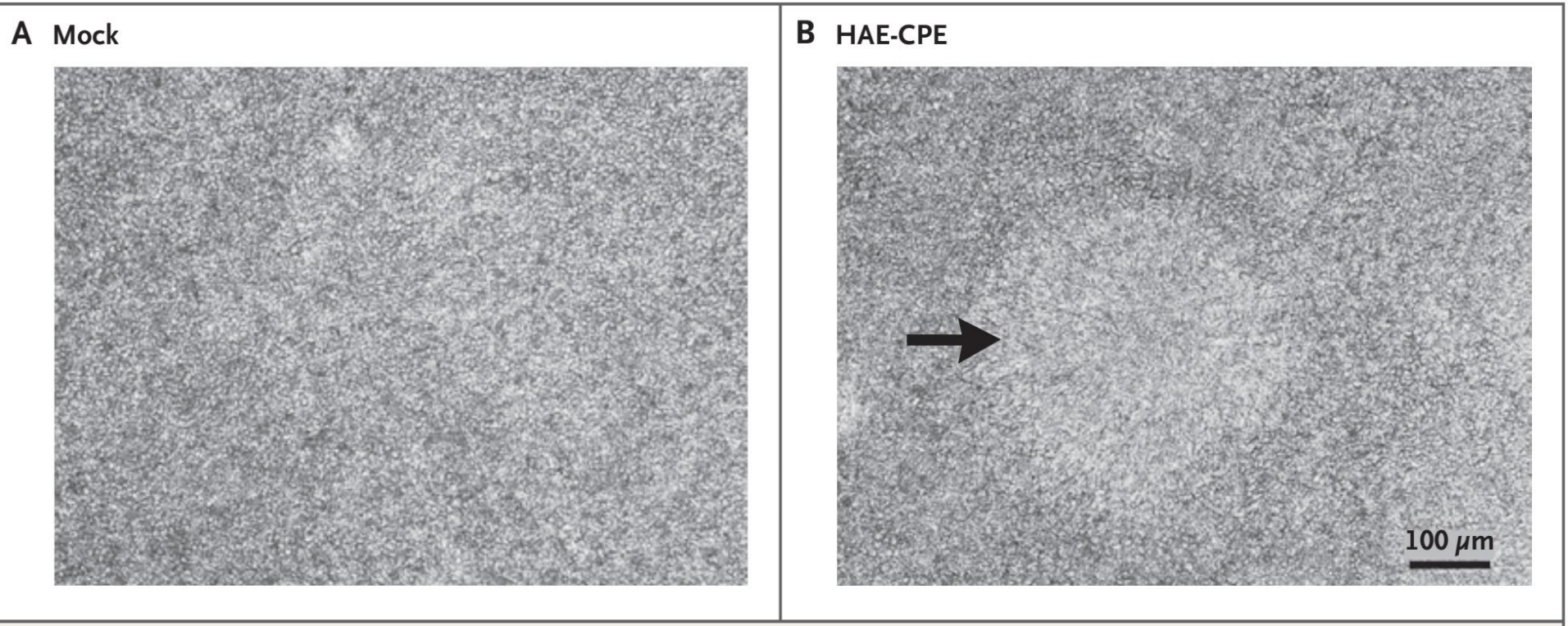


Figure 2. Cytopathic Effects in Human Airway Epithelial Cell Cultures after Inoculation with 2019-nCoV.

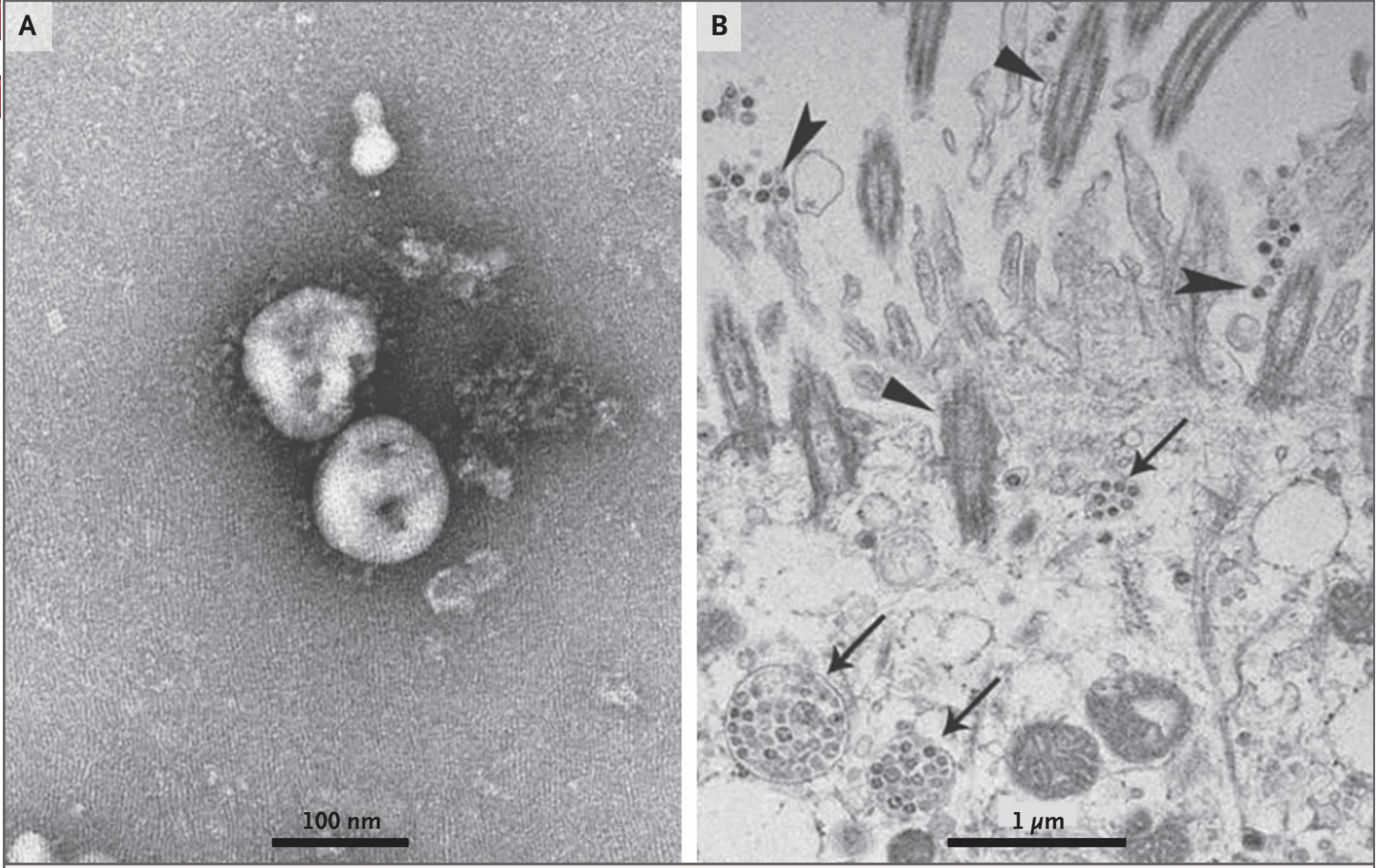


Figure 3. Visualization of 2019-nCoV with Transmission Electron Microscopy.

Negative-stained 2019-nCoV particles are shown in Panel A, and 2019-nCoV particles in the human airway epithelial cell ultrathin sections are shown in Panel B. Arrowheads indicate extracellular virus particles, arrows indicate inclusion bodies formed by virus components, and triangles indicate cilia.

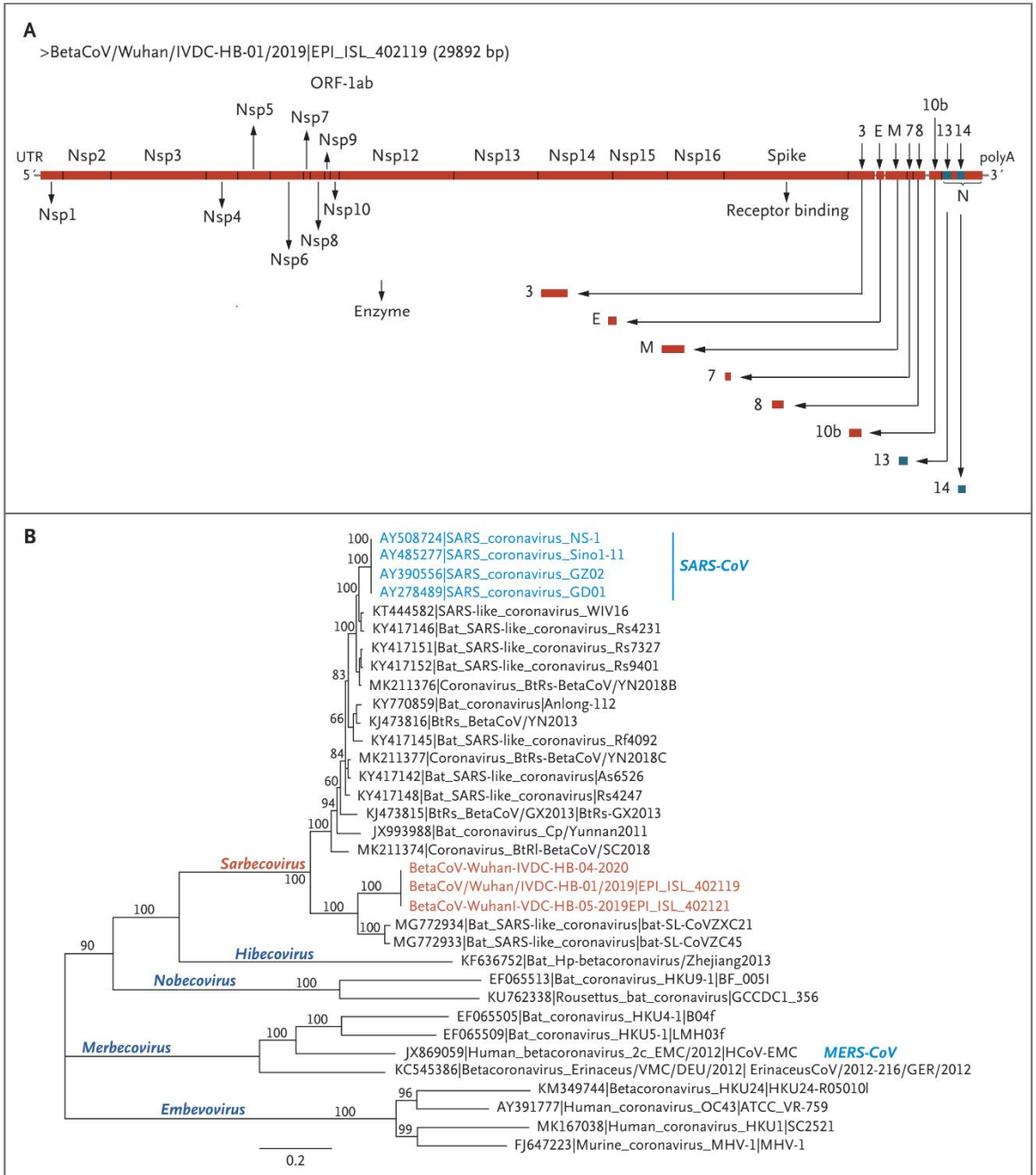
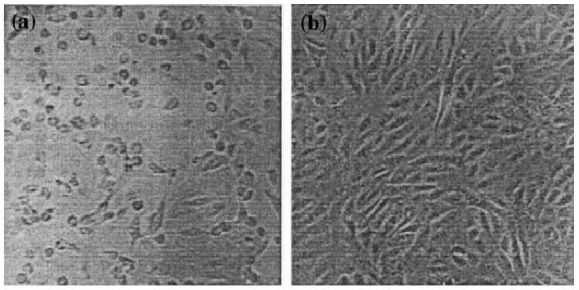


Figure 4. Schematic of 2019-nCoV and Phylogenetic Analysis of 2019-nCoV and Other Betacoronavirus Genomes.

Shown are a schematic of 2019-nCoV (Panel A) and full-length phylogenetic analysis of 2019-nCoV and other betacoronavirus genomes in the Orthocoronavirinae subfamily (Panel B).

"We propagate and isolate the virus in laboratory conditions from the patient who was positive for SARS-COV-2," said a biologist at the Clinic for Infectious Diseases "Dr. Fran Mihaljevic"**dr.sc. Željka Mačak Šafranko**.



The isolated virus was sent to Germany

The isolated virus was sent to Germany at day after the earthquake that hit Zagreb. The office was completely destroyed. "To get an isolate from Croatia is very important to us because once we find that a substance can work against viruses, we have to prove that that substance doesn't just work against local viruses, but worldwide," said team leader at Helmholtz. Center for Infectious Research in Germany, **Luka Čičin-Šain.**

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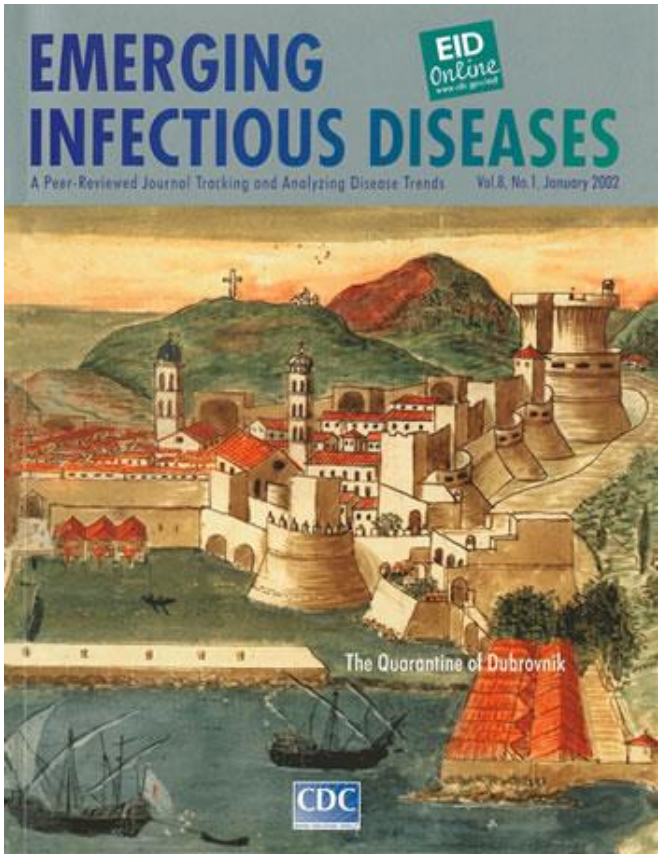
Epidemiologija

On 9 January 2020, ECDC published a Threat Assessment Brief on the cluster of pneumonia possibly associated with a novel coronavirus in Wuhan, China.
On 17 January 2020, ECDC published its first risk assessment on the novel coronavirus.
By 20 January 2020, there were reports of **confirmed cases from three countries outside China: Thailand, Japan and South Korea** [4]. These cases had all been exported from China.
On 23 January 2020, Wuhan City was **locked down** – with all travel in and out of Wuhan prohibited – and movement inside the city was restricted [5].
On 24 January 2020, the first European case was reported in France. This case had a travel history to China [6].



Objavljeno: 25.02.2020.

Prvi oboljeli od koronavirusa u Hrvatskoj je stabilno, ima blage simptome i nalazi se pod nadzorom

U banskim dvorima održan je danas sastanak Nacionalnog stožera za civilnu zaštitu. Nakon sastanka, predsjednik Vlade Andrej Plenković je na konferenciji za medije izvijestio da je u Hrvatskoj potvrđen prvi slučaj pacijenta oboljelog od koronavirusa.

„Novost koju smo dobili tijekom sastanka stožera je da imamo prvog pacijenta kojem je potvrđen koronavirus. Pacijent se nalazi u Zagrebu u Klinici za infektivne bolesti „Dr. Fran Mihaljević". Riječ je o mlađem čovjeku, ima blaži oblik bolesti, izoliran je i njegovo stanje je zasad dobro", kazao je predsjednik Vlade.

Plenković je rekao da će se Nacionalni stožer za civilnu zaštitu – kojeg će voditi potpredsjednik Vlade i ministar unutarnjih poslova Davor Božinović – sastajati koliko bude potrebno kako bi koordinirao sve aktivnosti.

Najavio je da će potpredsjednik Vlade Božinović u srijedu sazvati načelnike županijskih stožera civilne zaštite, kako bi se i oni uključili u sve aktivnosti vezane za prevenciju širenja koronavirusa.

„S obzirom na događanja u Italiji, osigurat ćemo da sve nadležne službe – od Ministarstva zdravstva, Ministarstva unutarnjih poslova, Državnog inspektorata, svih nadležnih tijela, osobito epidemioloških – budu u punoj pripravnosti i budu aktivni u sprječavanju širenja koronavirusa", kazao je.

Sve nadležne službe maksimalno angažirane

World Health Organization

REGIONAL OFFICE FOR Europe

I support contact tracing to fight the COVID-19 pandemic.

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SCIENTIFIC REPORTS
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OPEN

Molecular epidemiology of the first wave of severe acute respiratory syndrome coronavirus 2 infection in Thailand in 2020

Jiratchaya Puenpa[1,6], Kamol Suwannakarn[2,6], Jira Chansaenroj[1], Pornjarim Nilyanimit[1], Ritthideach Yorsaeng[1], Chompoonut Auphimai[1], Rungrueng Kitphati[3], Anek Mungaomklang[3], Amornmas Kongklieng[3], Chintana Chirathaworn[4], Nasamon Wanlapakorn[1,5] & Yong Poovorawan[1]✉

The coronavirus disease 2019 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major global concern. Several SARS-CoV-2 gene mutations have been reported. In the current study associations between SARS-CoV-2 gene variation and exposure history during the first wave of the outbreak in Thailand between January and May 2020 were investigated. Forty samples were collected at different time points during the outbreak, and parts of the SARS-CoV-2 genome sequence were used to assess genomic variation patterns. The phylogenetics of the 40 samples were clustered into L, GH, GR, O and T types. T types were predominant in Bangkok during the first local outbreak centered at a boxing stadium and entertainment venues in March 2020. Imported cases were infected with various types, including L, GH, GR and O. In southern Thailand introductions of different genotypes were identified at different times. No clinical parameters were significantly associated with differences in genotype. The results indicated local transmission (type T, Spike protein (A829T)) and imported cases (types L, GH, GR and O) during the first wave in Thailand. Genetic and epidemiological data may contribute to national policy formulation, transmission tracking and the implementation of measures to control viral spread.

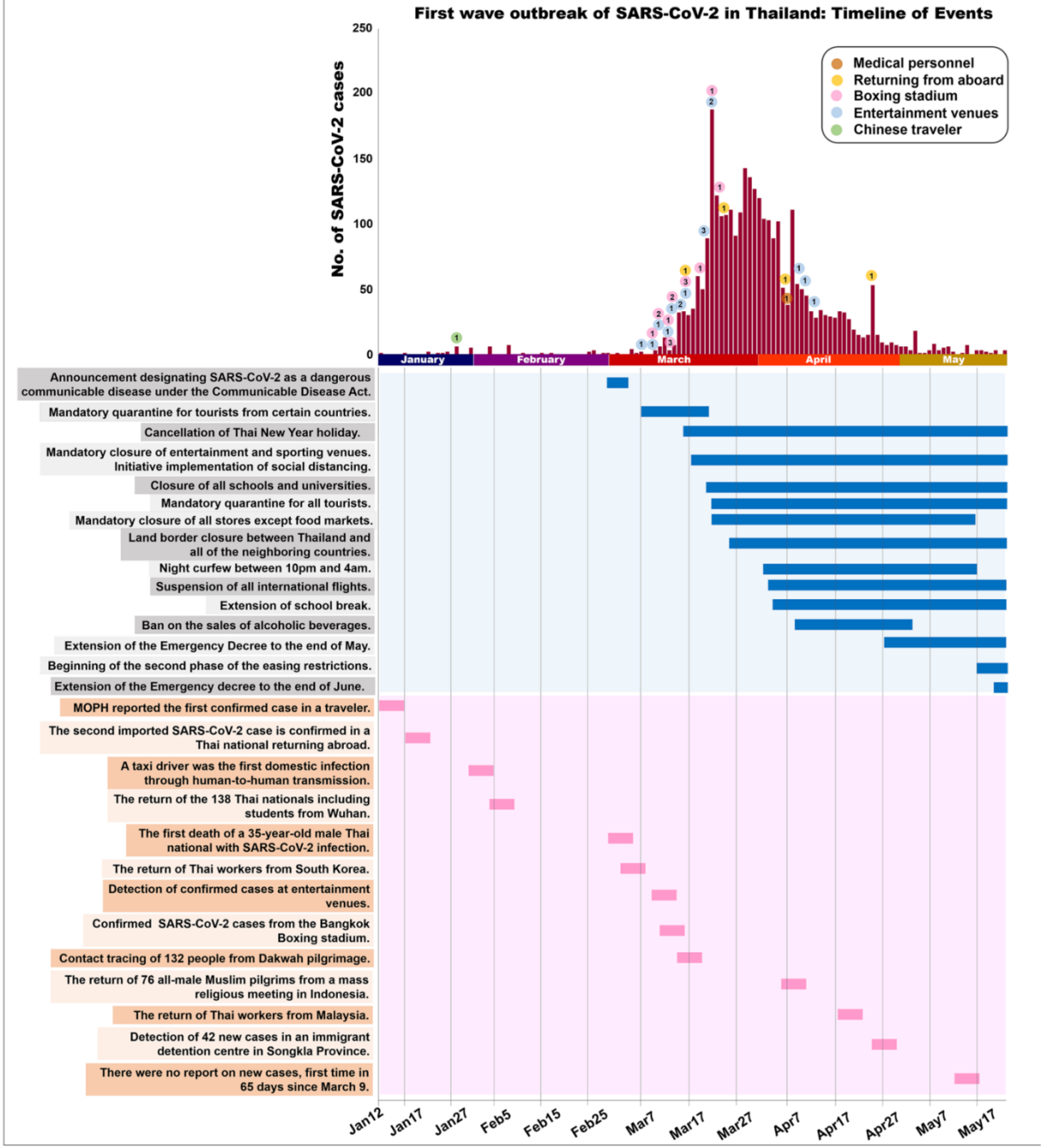
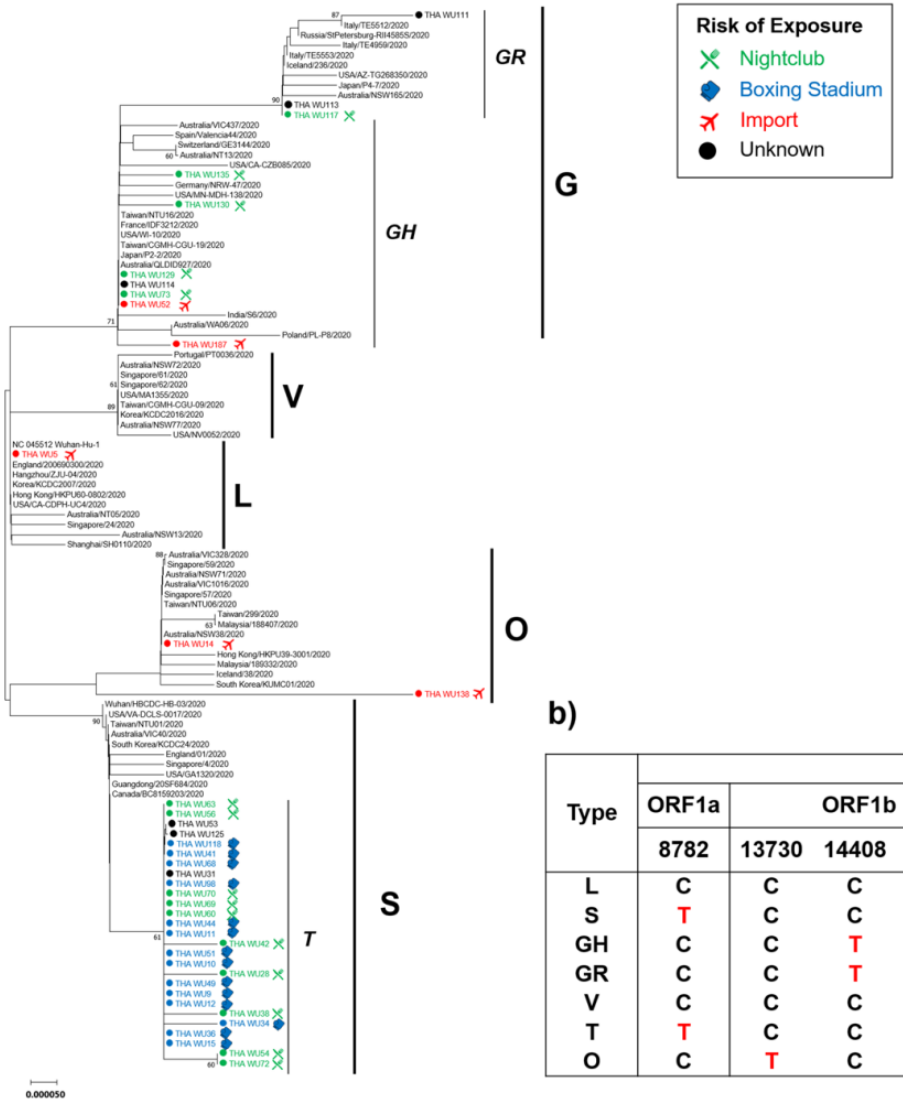


Figure 1. The first wave of SARS-CoV-2 outbreak in Thailand: Timeline of Events and the number of specimens.

a)



b)

Type	Nucleotide positions										
	ORF1a	ORF1b			S			ORF3a	ORF8	ORF9b	ORF14
	8782	13730	14408	14805	23403	23929	24047	26144	28144	28311	2881-3
L	C	C	C	C	A	C	G	G	T	C	GGG
S	T	C	C	C	A	C	G	G	C	C	GGG
GH	C	C	T	C	G	C	G	G	T	C	GGG
GR	C	C	T	C	G	C	G	G	T	C	AAC
V	C	C	C	T	A	C	G	T	T	C	GGG
T	T	C	C	C	A	C	A	G	C	C	GGG
O	C	T	C	C	A	T	G	G	T	T	GGG

Figure 2. Type of viral variations with exposure history. (**a**) Phylogenetic tree of concatenated sequences, including partial ORF1ab (nucleotide position 8,596–8,927 and 13,259–16,269), S (nucleotide position 21,320–25,541), ORF3a to E (nucleotide position 25,902–26,549), and ORF9b to ORF10 (nucleotide position 28,101–29,682). The phylogenetic tree was generated by the neighbor-joining method with 1,000 bootstrap replicates. Branch values > 60 were indicated. The blanket showed the five main types. Dots and colors precede the sequences isolated in this study with different risks of exposure. b) The pattern of nucleotide substitution change and type of SARS-CoV-2.

pathogens

MDPI

Article

Molecular Epidemiology Surveillance of SARS-CoV-2: Mutations and Genetic Diversity One Year after Emerging

Alejandro Flores-Alanis [1], Armando Cruz-Rangel [2], Flor Rodríguez-Gómez [3], James González [4], Carlos Alberto Torres-Guerrero [5], Gabriela Delgado [1], Alejandro Cravioto [1] and Rosario Morales-Espinosa [1,*]

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Abstract: In December 2019, the first cases of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were identified in the city of Wuhan, China. Since then, it has spread worldwide with new mutations being reported. The aim of the present study was to monitor the changes in genetic diversity and track non-synonymous substitutions (*dN*) that could be implicated in the fitness of SARS-CoV-2 and its spread in different regions between December 2019 and November 2020. We analyzed 2213 complete genomes from six geographical regions worldwide, which were downloaded from GenBank and GISAID databases. Although SARS-CoV-2 presented low genetic diversity, there has been an increase over time, with the presence of several hotspot mutations throughout its genome. We identified seven frequent mutations that resulted in *dN* substitutions. Two of them, C14408T>P323L and A23403G>D614G, located in the nsp12 and Spike protein, respectively, emerged early in the pandemic and showed a considerable increase in frequency over time. Two other mutations, A1163T>I120F in nsp2 and G22992A>S477N in the Spike protein, emerged recently and have spread in Oceania and Europe. There were associations of P323L, D614G, R203K and G204R substitutions with disease severity. Continuous molecular surveillance of SARS-CoV-2 will be necessary to detect and describe the transmission dynamics of new variants of the virus with clinical relevance. This information is important to improve programs to control the virus.

Citation: Flores-Alanis, A.; Cruz-Rangel, A.; Rodríguez-Gómez, F.; González, J.; Torres-Guerrero, C.A.; Delgado, G.; Cravioto, A.; Morales-Espinosa, R. Molecular Epidemiology Surveillance of SARS-CoV-2: Mutations and Genetic Diversity One Year after Emerging. *Pathogens* **2021**, *10*, 184. https://doi.org/10.3390/pathogens10020184

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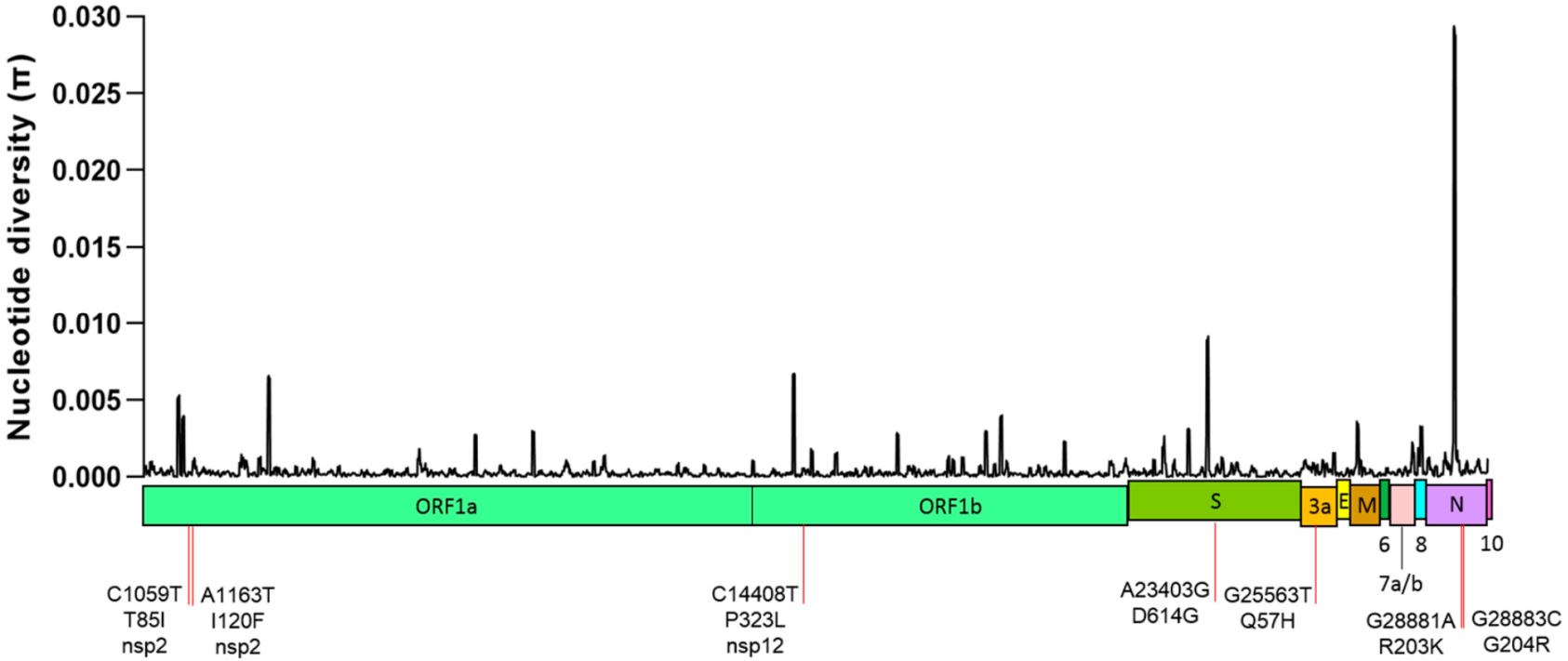

Figure 1. Nucleotide diversity (π) in a total of 2213 SARS-CoV-2 genomes. Several hotspot mutations were detected along the genome. Seven nucleotide substitutions with frequencies > 10% in the sample population are indicated, all of which resulted in amino acid non-synonymous (*dN*) substitutions. The π values were calculated within a sliding window of 50 bp moving with 10 bp steps.

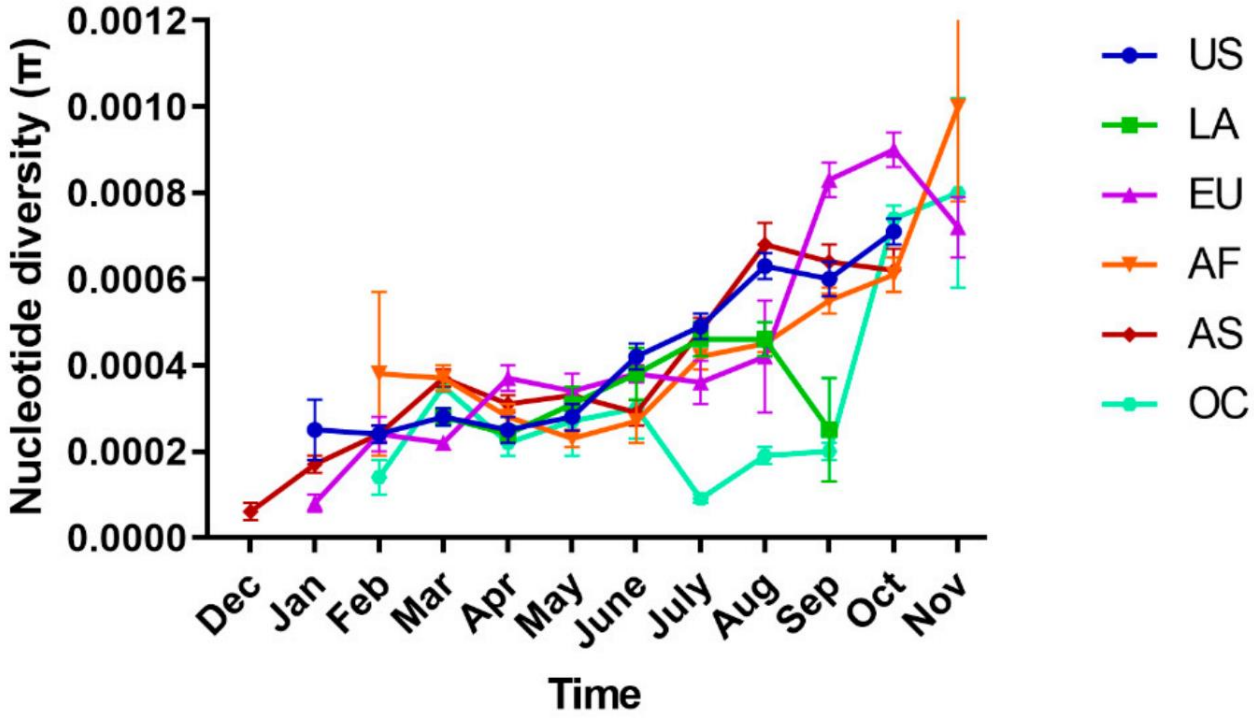

Figure 3. Temporal changes of SARS-Cov-2 nucleotide diversity (π) by region. Abbreviations: Dec, December; Jan, January, Feb, February, Mar, March; Apr, April; Aug, August; Sep, September; Oct, October; Nov, November. US, United States of America; LA, Latin America; EU, Europe; AF, Africa; AS, Asia; OC, Oceania.

Earthquake in the time of COVID-19: The story from Croatia (CroVID-20)

Rok Čivljak[1,2], Alemka Markotić[1,3,4], Krunoslav Capak[2,5]

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[3] Catholic University of Croatia, Zagreb, Croatia
[4] Faculty of Medicine of the University of Rijeka, Rijeka, Croatia
[5] Croatian Institute of Public Health, Zagreb, Croatia

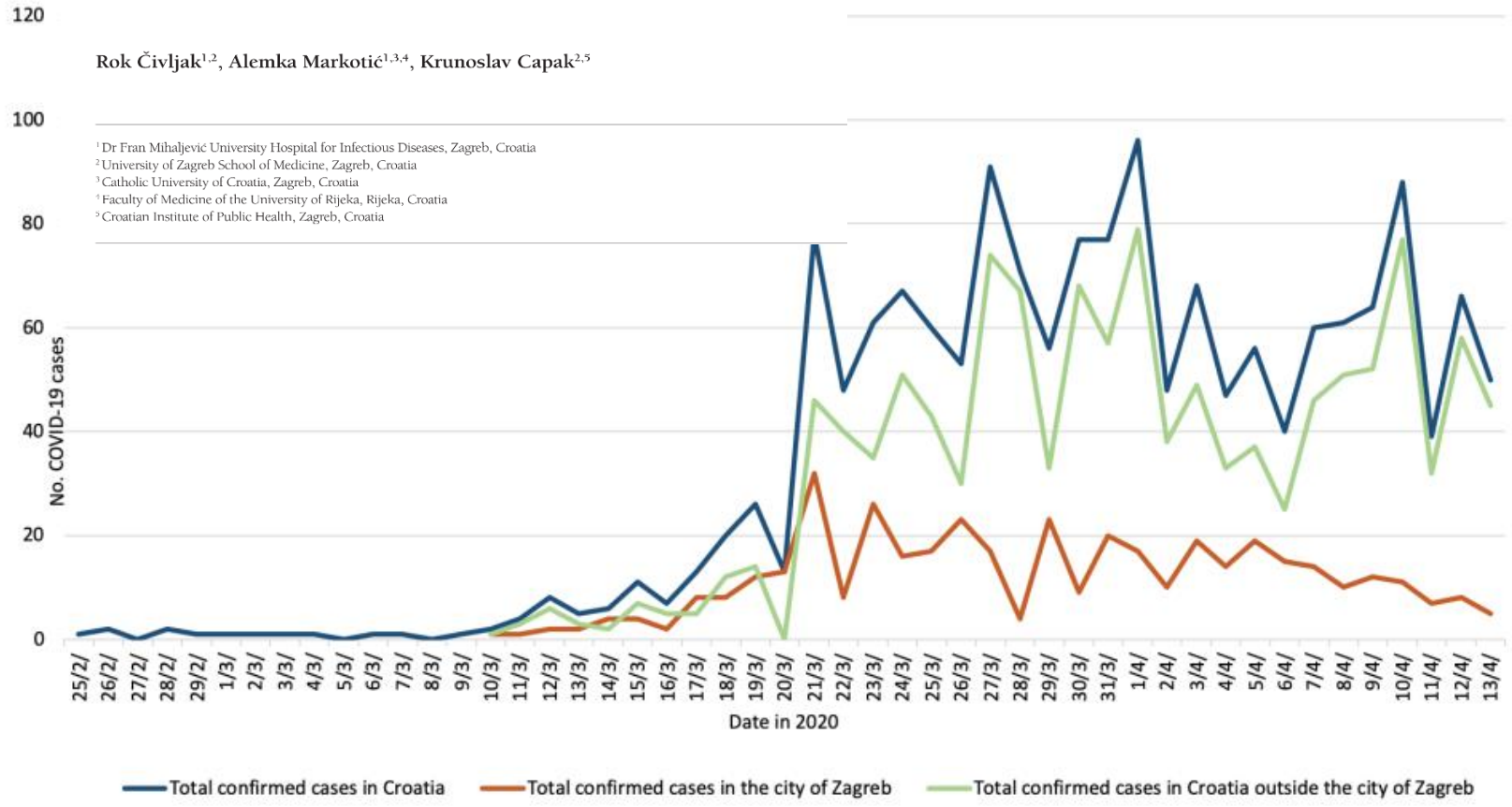

Figure 1. The number of confirmed COVID-19 cases in Croatia and the city of Zagreb six weeks since the first COVID-19 case and three weeks after the earthquake.

extensively damaged hospital buildings (authors' photo archive, used with permission).

Dijagnostika

RESEARCH

Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR

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Research

Detection real-time I V) by

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RT-PCR. Euro Surveill. 2020;25

chneider Julia, Schmidt Marie
Louis, Ellis Joanna, Zambon
s (2019-nCoV) by real-time

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Background: The ongoing outbreak of the recently emerged novel coronavirus (2019-nCoV) poses a challenge for public health laboratories as virus isolates are unavailable while there is growing evidence that the outbreak is more widespread than initially thought, and international spread through travellers does already occur. **Aim:** We aimed to develop and deploy robust diagnostic methodology for use in public health laboratory settings without having virus material available. **Methods:** Here we present a validated diagnostic workflow for 2019-nCoV, its design relying on close genetic relatedness of 2019-nCoV with SARS coronavirus, making use of synthetic nucleic acid technology. **Results:** The workflow reliably detects 2019-nCoV, and further discriminates 2019-nCoV from SARS-CoV. Through coordination between academic and public laboratories, we confirmed assay exclusivity based on 297 original clinical specimens containing a full spectrum of human respiratory viruses. Control material is made available through European Virus Archive – Global (EVAg), a European Union infrastructure project. **Conclusion:** The present study demonstrates the enormous response capacity achieved through coordination of academic and public laboratories in national and European research networks.

OVO JE ČOVJEK KOJI ĆE PRVI ZNATI JE LI KORONAVIRUS DOŠAO U HRVATSKU 'Sve možemo otkriti za najviše 8 sati'

AUTOR: Goranka Jureško OBJAVLJENO: 03.02.2020. u 16:30

Ivan Christian Kurolt


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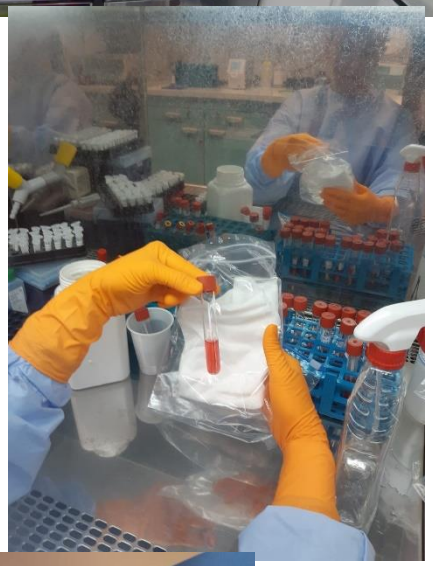


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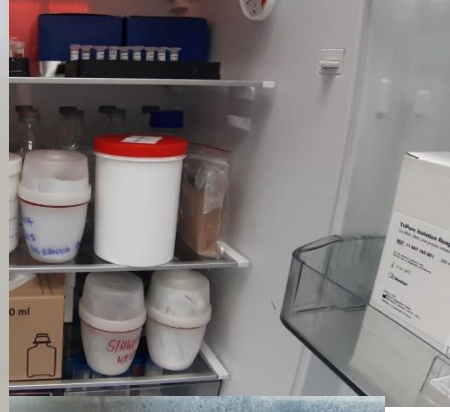

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ORIGINAL ARTICLE

Antibody response and the clinical presentation of patients with COVID-19 in Croatia: the importance of a two-step testing approach

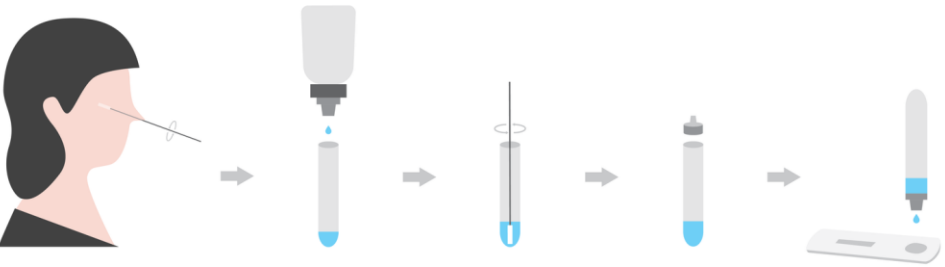
Oktavija Đaković Rode[1,2] · Ivan-Christian Kurolt[1] · Ivan Puljiz[1,3] · Rok Čivljak[1,3] · Nataša Cetinić Balent[1] · Renata Laškaj[1] · Mirjana Kujundžić Tiljak[3,4] · Radojka Mikulić[1] · Alemka Markotić[1,5,6]

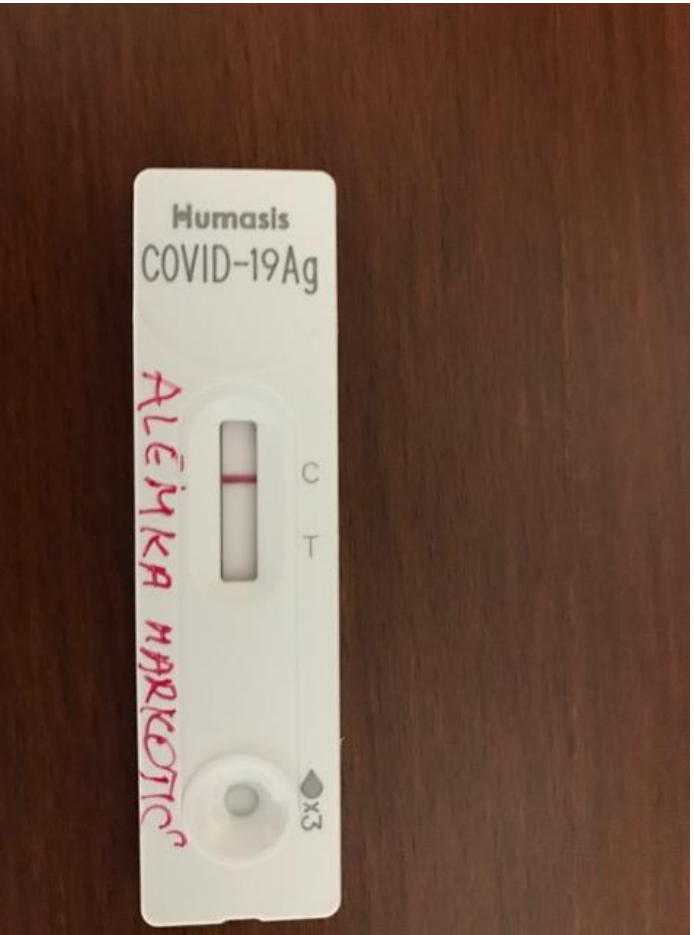
Received: 26 June 2020 / Accepted: 24 August 2020

Abstract

According to anti-SARS-CoV-2 seroresponse in patients with COVID-19 from Croatia, we emphasised the issue of different serological tests and need for combining diagnostic methods for COVID-19 diagnosis. Anti-SARS-CoV-2 IgA and IgG ELISA and IgM/IgG immunochromatographic assay (ICA) were used for testing 60 sera from 21 patients (6 with severe, 10 moderate, and 5 with mild disease). The main clinical, demographic, and haemato-biochemical data were analysed. The most common symptoms were cough (95.2%), fever (90.5%), and fatigue and shortness of breath (42.9%). Pulmonary opacities showed 76.2% of patients. Within the first 7 days of illness, seropositivity for ELISA IgA and IgG was 42.9% and 7.1%, and for ICA IgM and IgG 25% and 10.7%, respectively. From day 8 after onset, ELISA IgA and IgG seropositivity was 90.6% and 68.8%, and for ICA IgM and IgG 84.4% and 75%, respectively. In general, sensitivity for ELISA IgA and IgG was 68.3% and 40%, and for ICA IgM and IgG 56.7% and 45.0%, respectively. The anti-SARS-CoV-2 antibody distributions by each method were statistically different (ICA IgM vs. IgG, $p = 0.016$; ELISA IgG vs. IgA, $p < 0.001$). Antibody response in COVID-19 varies and depends on the time the serum is taken, on the severity of disease, and on the type of test used. IgM and IgA antibodies as early-stage disease markers are comparable, although they cannot replace each other. Simultaneous IgM/IgG/IgA anti-SARS-CoV-2 antibody testing followed by the confirmation of positive findings with another test in a two-tier testing is recommended.

Keywords COVID-19 diagnostics · Clinical and laboratory findings · Anti-SARS-CoV-2 antibody response · Serological methods · Two-step testing approach · Croatia





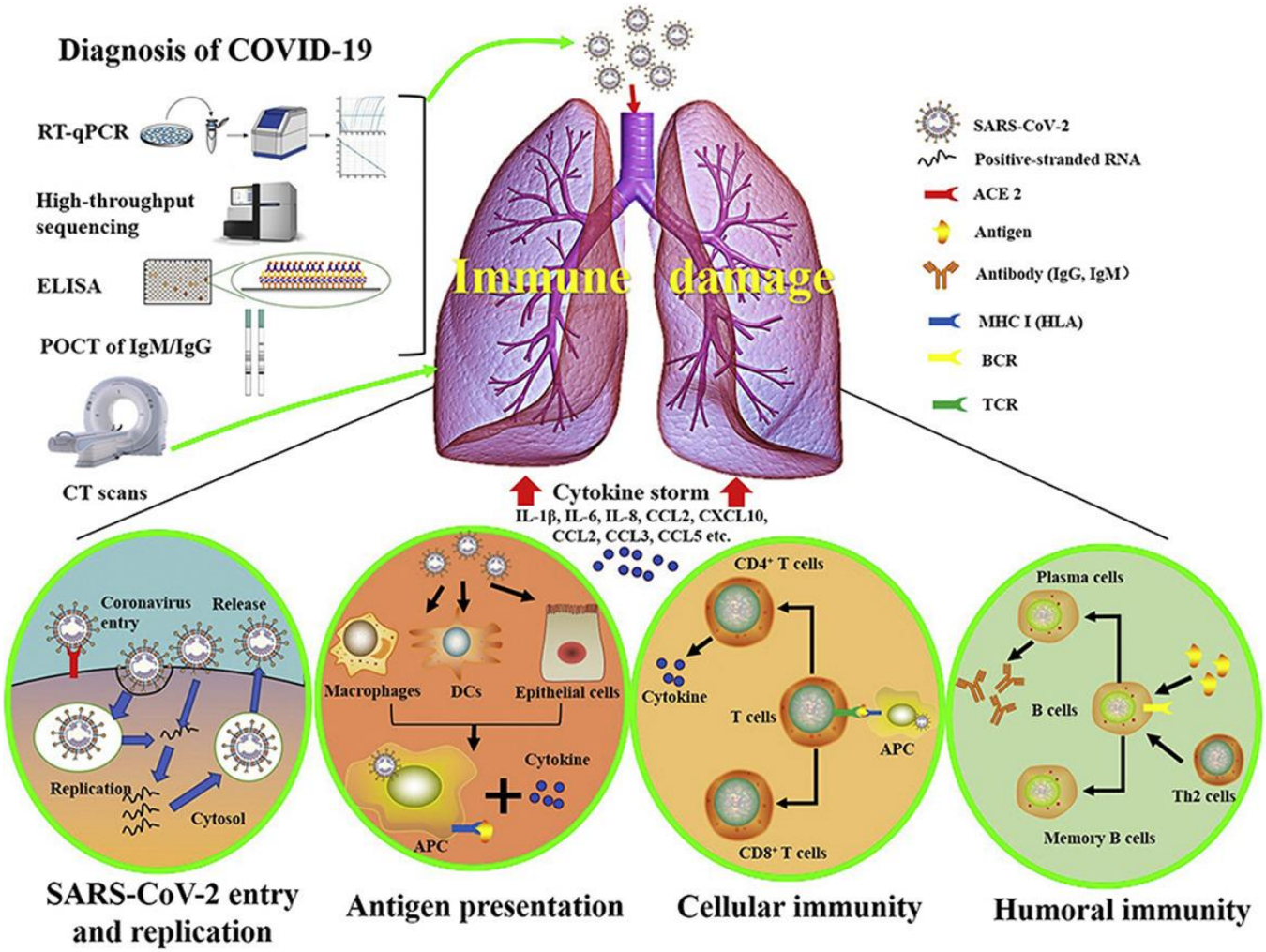
RESEARCH

Isolation, Sequence, Infectivity, and Replication Kinetics of Severe Acute Respiratory Syndrome Coronavirus 2

Arinjay Banerjee, Jalees A. Nasir,[1] Patrick Budylowski,[1] Lily Yip, Patryk Aftanas, Natasha Christie, Ayoob Ghalami, Kaushal Baid, Amogelang R. Raphenya, Jeremy A. Hirota, Matthew S. Miller, Allison J. McGeer, Mario Ostrowski, Robert A. Kozak, Andrew G. McArthur, Karen Mossman, Samira Mubareka

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 26, No. 9, September 2020

Imunopatogeneza



Signal Transduction and Targeted Therapy

www.nature.com/sigtrans

REVIEW ARTICLE OPEN

COVID-19: immunopathogenesis and Immunotherapeutics

Li Yang[1], Shasha Liu[1], Jinyan Liu[1], Zhixin Zhang[2], Xiaochun Wan[3], Bo Huang[4], Youhai Chen[5] and Yi Zhang[1]

The recent novel coronavirus disease (COVID-19) outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is seeing a rapid increase in infected patients worldwide. The host immune response to SARS-CoV-2 appears to play a critical role in disease pathogenesis and clinical manifestations. SARS-CoV-2 not only activates antiviral immune responses, but can also cause uncontrolled inflammatory responses characterized by marked pro-inflammatory cytokine release in patients with severe COVID-19, leading to lymphopenia, lymphocyte dysfunction, and granulocyte and monocyte abnormalities. These SARS-CoV-2-induced immune abnormalities may lead to infections by microorganisms, septic shock, and severe multiple organ dysfunction. Therefore, mechanisms underlying immune abnormalities in patients with COVID-19 must be elucidated to guide clinical management of the disease. Moreover, rational management of the immune responses to SARS-CoV-2, which includes enhancing anti-viral immunity while inhibiting systemic inflammation, may be key to successful treatment. In this review, we discuss the immunopathology of COVID-19, its potential mechanisms, and clinical implications to aid the development of new therapeutic strategies against COVID-19.

Signal Transduction and Targeted Therapy (2020)5:128 ; https://doi.org/10.1038/s41392-020-00243-2

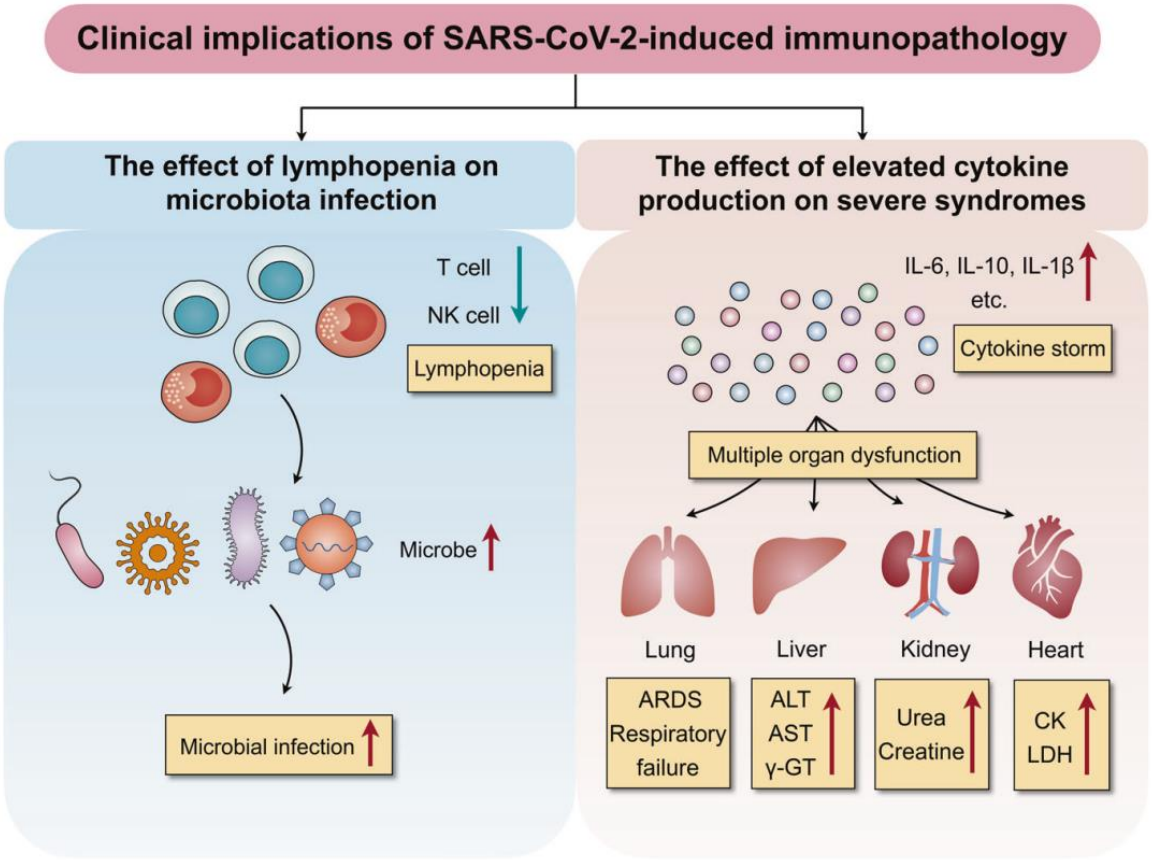


Fig. 3 Clinical implications of SARS-CoV-2-induced immunopathology. Patients with COVID-19 and presenting with lymphopenia are more prone to infections with the microbe, which leads to disease progression and increased severity. In addition, cytokine storms can initiate inflammatory-induced multiple organ dysfunction, including lung injury that can lead to ARDS, respiratory failure, liver injury with alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamine transferase (γ-GT) upregulation, kidney injury with increased urea and creatine levels, and heart injury with increased creatine kinase (CK) and lactate dehydrogenase (LDH) levels

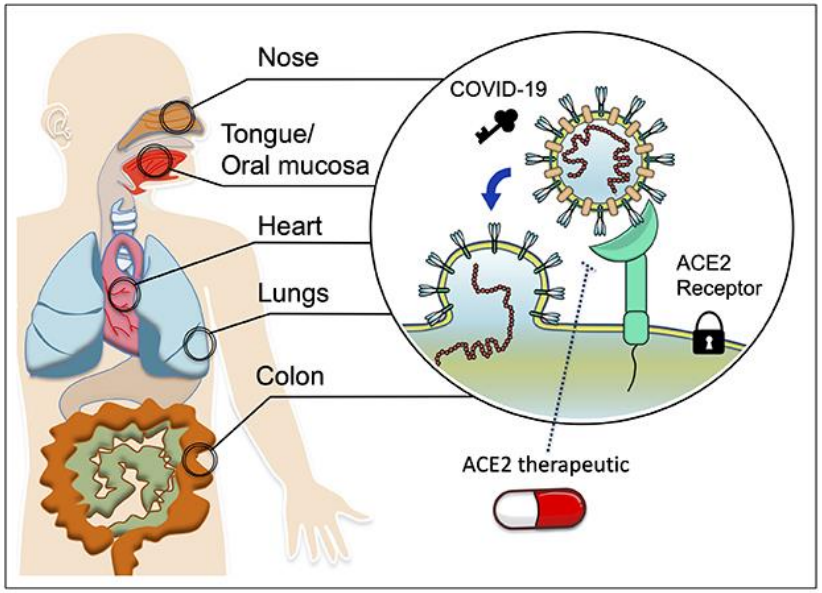
Klinička slika
Zarazna bolest s brojnim licima

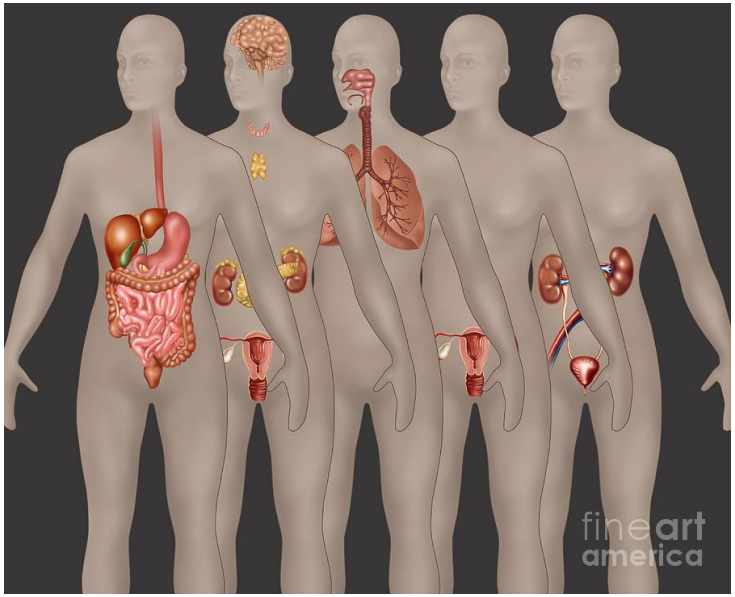
Asimptomatski

Blagi

Srednje teški

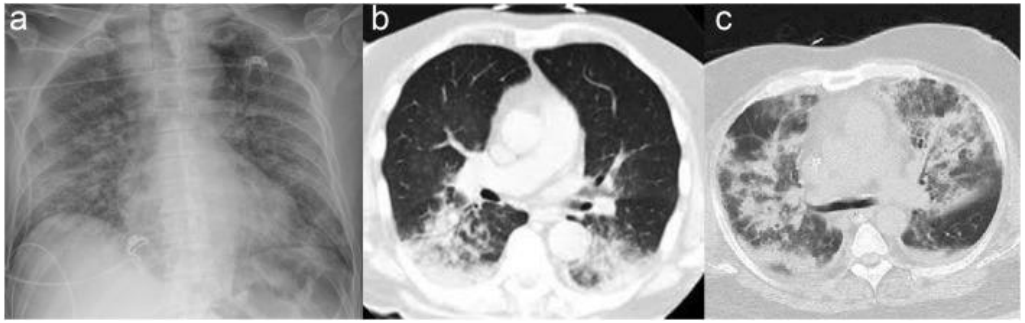
Teški





On 27 April 2020, health authorities in the UK warned of a number of seriously ill children with multisystem inflammatory syndrome associated with COVID-19, presenting with signs of circulatory shock and hyperinflammatory state, with features consistent with toxic shock or Kawasaki disease [12].

AKUTNI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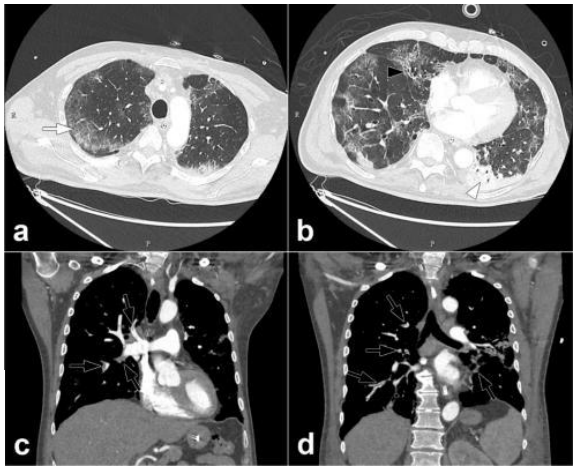
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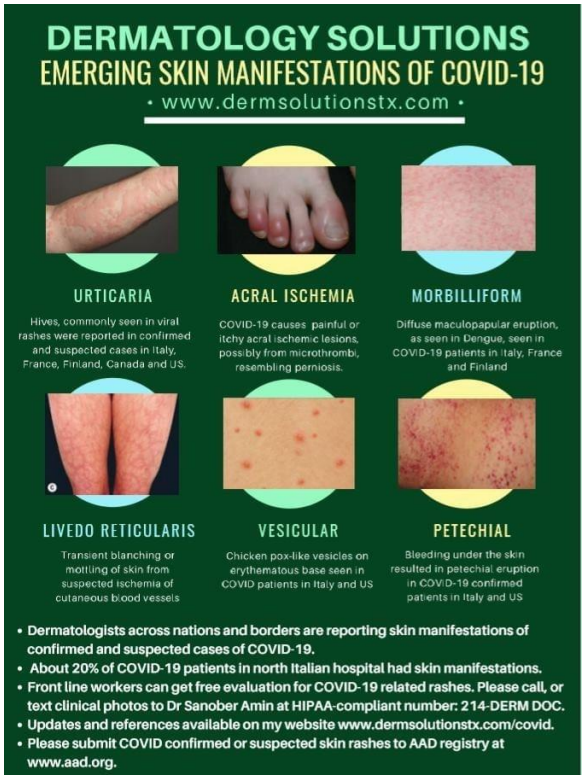
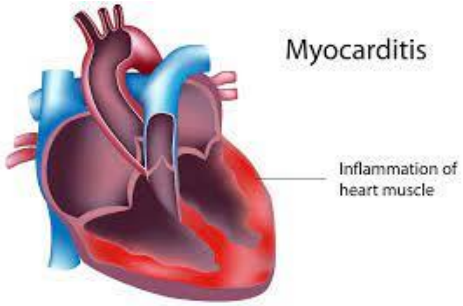
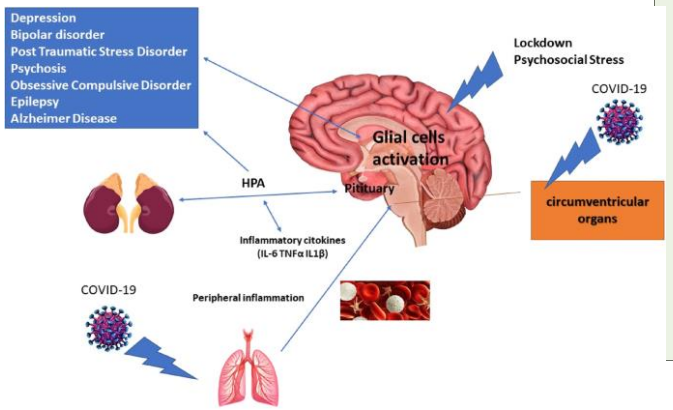

DERMATOLOGY SOLUTIONS
EMERGING SKIN MANIFESTATIONS OF COVID-19
• www.dermsolutionstx.com •
URTICARIA
Hives, commonly seen in viral rashes were reported in confirmed and suspected cases in Italy, France, Finland, Canada and US.
ACRAL ISCHEMIA
COVID-19 causes painful or itchy acral ischemic lesions, possibly from microthrombi, resembling perniosis.
MORBILLIFORM
Diffuse maculopapular eruption, as seen in Dengue, seen in COVID-19 patients in Italy, France and Finland
LIVEDO RETICULARIS
Transient blanching or mottling of skin from suspected ischemia of cutaneous blood vessels
VESICULAR
Chicken pox-like vesicles on erythematous base seen in COVID patients in Italy and US
PETECHIAL
Bleeding under the skin resulted in petechial eruption in COVID-19 confirmed patients in Italy and US
• Dermatologists across nations and borders are reporting skin manifestations of confirmed and suspected cases of COVID-19.
• About 20% of COVID-19 patients in north Italian hospital had skin manifestations.
• Front line workers can get free evaluation for COVID-19 related rashes. Please call, or text clinical photos to Dr Sanober Amin at HIPAA-compliant number: 214-DERM DOC.
• Updates and references available on my website www.dermsolutionstx.com/covid.
• Please submit COVID confirmed or suspected skin rashes to AAD registry at www.aad.org.


Myocarditis
Inflammation of heart muscle


Depression
Bipolar disorder
Post Traumatic Stress Disorder
Psychosis
Obsessive Compulsive Disorder
Epilepsy
Alzheimer Disease
Lockdown
Psychosocial Stress
COVID-19
Glial cells activation
Pituitary
HPA
circumventricular organs
Inflammatory citokines (IL-6 TNFα IL1β)
COVID-19
Peripheral inflammation

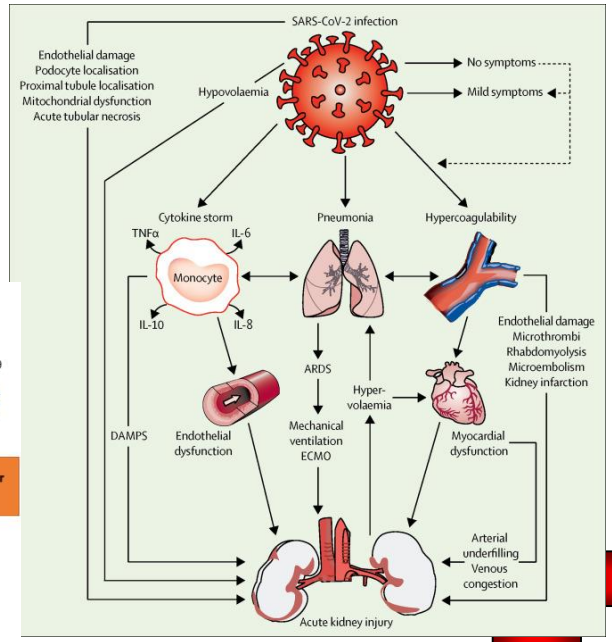

SARS-CoV-2 infection
Endothelial damage
Podocyte localisation
Proximal tubule localisation
Mitochondrial dysfunction
Acute tubular necrosis
Hypovolaemia
No symptoms
Mild symptoms
Cytokine storm
Pneumonia
Hypercoagulability
TNFα
IL-6
Monocyte
IL-10
IL-8
Endothelial damage
Microthrombi
Rhabdomyolysis
Microembolism
Kidney infarction
ARDS
Hyper-volaemia
DAMPS
Endothelial dysfunction
Mechanical ventilation ECMO
Myocardial dysfunction
Arterial underfilling
Venous congestion
Acute kidney injury

Table 1 General characteristics and clinical findings in 21 patients with confirmed COVID-19

Patient characteristics	No. = 21 (%)
Age median (range), years	56 (26–81)
Male/female	13 (61.9)/8 (38.1)
Comorbidity	10 (47.6)
Mild disease	5 (23.8)
Moderate disease	10 (47.6)
Severe disease	6 (28.6)
Respiratory symptoms	
Cough	20 (95.2)
Fatigue	9 (42.9)
Shortness of breath	9 (42.9)
Sputum production	5 (23.8)
Sore throat	3 (14.3)
Nasal congestion	2 (9.5)
Systemic symptoms	
Fever (temperature > 38.0 °C)	19 (90.5)
Chills	8 (38.1)
Myalgia and arthralgia	7 (33.3)
Headache	5 (23.8)
Diarrheal	4 (19.1)
Nausea or vomiting	3 (14.3)
New loss of smell	1 (4.8)
Imaging	
Chest radiography	21 (100)
Chest computed tomography	3 (14.3)
Chest radiography abnormalities	16 (76.2)
Antiviral treatment	
Yes	17 (81.0)
Lopinavir/ritonavir	2 (9.5)
Hydroxychloroquine	6 (28.6)
Hydroxychloroquine plus azithromycin	9 (42.9)
No	4 (19.1)

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Hydroxychloroquine plus azithromycin	9 (42.9)
No	4 (19.1)

Table 2 The main clinical laboratory findings in 21 COVID-19 patients

Laboratory data (reference range)	Findings
White cell count: median (IQR) $\times 10^9$ ($3.4–9.7 \times 10^9$)	5.7 (4.6–6.7)
Lymphocyte count: median (IQR) $\times 10^9$ ($1.19–3.35 \times 10^9$)	1.1 (0.8–1.4)
Lymphocyte relative percent: median (IQR) % (20–46%)	20.5 (13.4–26.4)
Aspartate aminotransferase (AST) U/L: median (IQR) (8–30 U/L)	36 (20–55)
Alanine aminotransferase (ALT) U/L: median (IQR) (10–36 U/L)	31 (16–70)
Lactate dehydrogenase U/L: median (IQR) (< 241 U/L)	227 (176–292)
Creatine kinase (CK) U/L: median (IQR) (< 153 U/L)	101 (36–163)
C-reactive protein mg/L: median (IQR) (< 5.0 mg/L)	25.2 (6.9–64.0)

Effects of environmental factors on severity and mortality of COVID-19

Domagoj Kifer[1], Dario Bugada[2], Judit Villar-Garcia[3], Ivan Gudelj[4], Cristina Menni[5], Carole Sudre[5], Frano Vučković[4], Ivo Ugrina[4], Luca F Lorini[2], Silvia Bettinelli[2], Nicola Ughi[6], Alessandro Maloberti[6], Oscar Epis[6], Cristina Giannattasio[6] , Claudio Rossetti[6], Livije Kalogjera[7], Jasminka Peršec[8], Luke Ollivere[9], Benjamin J Ollivere[9], Huadong Yan[10,11], Ting Cai[12], Guruprasad Aithal[9], Claire J Steves[5], Igor Rudan[13], Ivica Lukšić[14], Alemka Markotić[15], Johannes Brachmann[16], Benjamin Murray[17], Sebastien Ourselin[17], Julio Pascual[2] Ana M. Valdes[9], Margarita Posso[3], Juan P Horcajada[3], Xavier Castells[3], Massimo Allegri[18], Dragan Primorac[19], Tim D. Spector[5], Clara Barrios[3], Gordan Lauc[1,4]

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[10] Department of Infectious Diseases, Key Laboratory of Diagnosis and Treatment of Digestive System Tumors of Zhejiang Province, Hwamei Hospital, University of Chinese Academy of Sciences, Ningbo 315010, China
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[12] Department of Infectious Diseases, Key Laboratory of Diagnosis and Treatment of Digestive System Tumors of Zhejiang Province, Hwamei Hospital, University of Chinese Academy of Sciences, Ningbo 315010, China
[13] University of Edinburgh, Edinburgh, UK
[14] School of Medicine University of Zagreb, University Hospital Dubrava, Zagreb, Croatia
[15] University Hospital for infectious Ddiseases "Fran Mihaljević", Zagreb, Croatia
[16] REGIOMED Kliniken, Coburg, Germany
[17] School of Biomedical Engineering & Imaging Sciences, King's College London, UK
[18] Pain Therapy Service Policlinico of Monza Hospital – Monza, Italy
[19] St. Catharine Hospital, Zagreb, Croatia & Eberly College of Science, Penn State University, USA & University of Split School of Medicine, Croatia & University of Osijek School of Medicine, Croatia & University of Osijek Faculty of Dental Medicine and Health, Croatia & Medical School REGIOMED, Coburg, Germany

KRONIČNI- *POST-COVID-19*

Nakon šest mjeseci post-COVID-19 praćenja, **76% svih pacijenata** imalo je barem jedan od navedenih simptoma:

umor / slabosti mišića (63%)

poteškoće sa spavanjem (26%)

gubitak kose (22%)

poteškoće s mirisom i okusom (11 i 9%)

problemi s mobilnošću (7%)

U multivarijabilnoj analizi, **žene i sudionici s težim oblikom bolesti** imaju veći rizik od:

oštećenja plućne difuzije i dugotrajnije RTG promjene

anksioznost ili depresiju

umor ili mišićnu slabost

i glavna su ciljna populacija za dugotrajno praćenje.

***Lancet* 2021 397220-232**


BIOHAZARD
KARANTENA

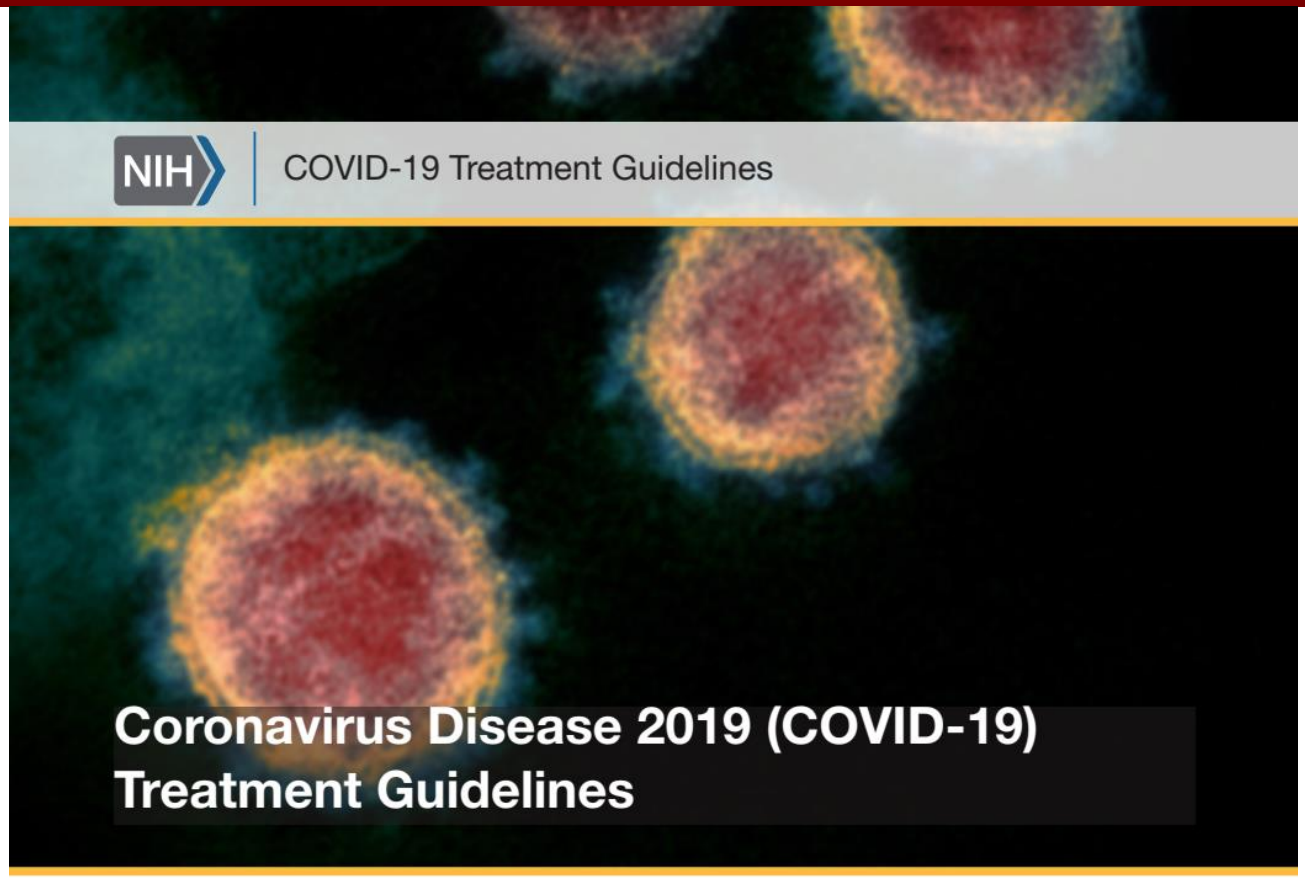

BIOHAZARD
KARANTENA
ZG







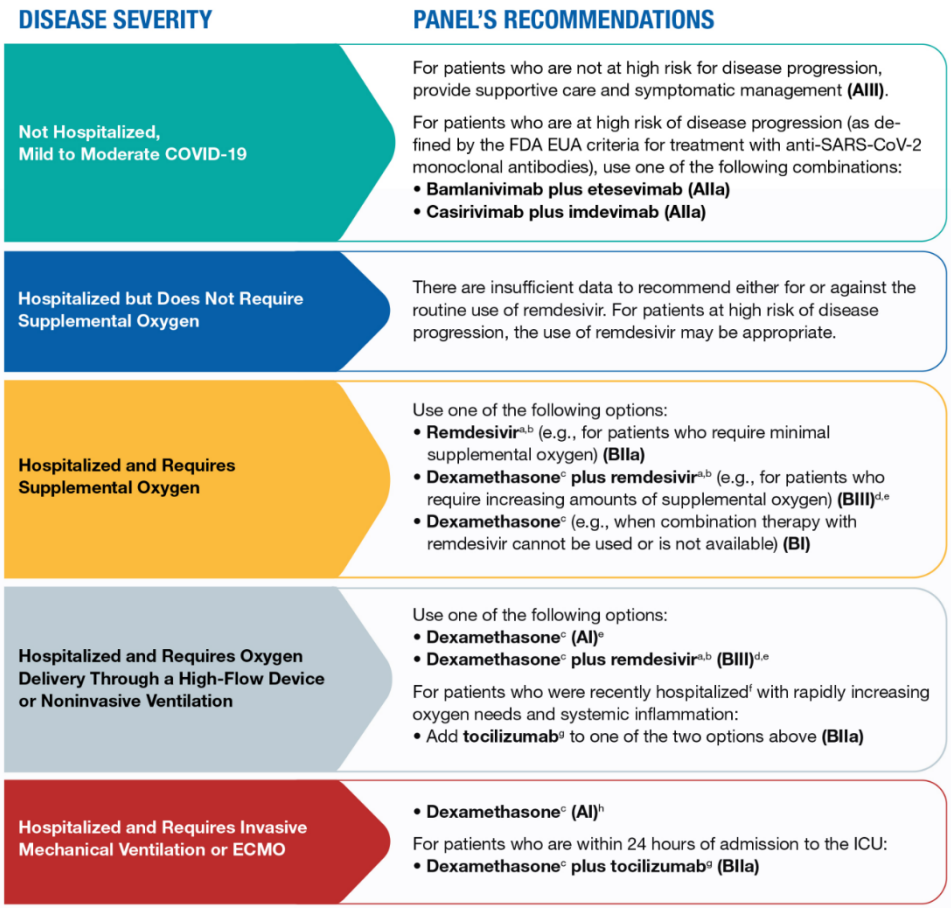
Liječenje



Credit NIAID-RML

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnotes.



Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] The remdesivir dose is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.

[b] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.

[c] The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.

[d] The combination of dexamethasone and remdesivir has not been studied in clinical trials.

[e] In the rare circumstances where corticosteroids cannot be used, **baricitinib plus remdesivir** can be used **(BIIa)**. The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.

[f] For example, within 3 days of hospital admission. See the Interleukin-6 Inhibitors section for more information.

[g] The tocilizumab dose is 8 mg/kg of actual body weight (up to 800 mg) administered as a single IV dose. Tocilizumab should not be combined with baricitinib and should be avoided in certain groups of patients who are at increased risk for complications. See the Interleukin-6 Inhibitors section for more information.

[h] The combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of remdesivir monotherapy in these patients.

Key: ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; ICU = intensive care unit; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

Smjernice za liječenje oboljelih od COVID-19

Početkom 2020. godine suočili smo se s pandemijom uzrokovanom novim koronavirusom (SARS-CoV- 2, od engl. severe acute respiratory syndrome coronavirus 2), uzročnikom nove bolesti koja je nazvana COVID-19 (od engl. coronavirus disease 2019).

U Hrvatskoj su do sada izdane:

- Smjernice Klinike za infektivne bolesti „Dr. Fran Mihaljević" u Zagrebu i Hrvatskoga društva za infektivne bolesti Hrvatskog liječničkog zbora (HLZ-a) za antivirusno i imunomodulacijsko liječenje oboljelih od COVID-19
- Smjernice Hrvatskoga društva za infektivne bolesti HLZ-a: „Kliničko zbrinjavanje pacijenata s COVID-19."

Na temelju članka 52. Zakona o sustavu državne uprave (Narodne novine br. 66/19), ministar zdravstva je dana 29. travnja 2020. godine donio odluku (KLASA: 011-02/20-01/194, UR. BROJ 534-02-2-2/1-20- 2 od 29. travnja) o osnivanju Povjerenstva za primjenu lijekova u liječenju i profilaksi COVID-19 uključujući antivirusne i imunomodulacijske lijekove, u skladu s postojećim znanstvenim dokazima i preporukama međunarodnih relevantnih institucija (u daljnjem tekstu: Povjerenstvo).

Povjerenstvo je osnovano zbog važnosti pravovremenog otkrivanja, dijagnosticiranja, zbrinjavanja i liječenja osoba zaraženih virusom SARS-CoV-2 i bolesnika s COVID-19, a u cilju uspješnog suzbijanja epidemije bolesti COVID-19 u Hrvatskoj.

U Povjerenstvo su imenovani sljedeći članovi: doc.dr.sc. Rok Čivljak, dr.med. (predsjednik), prof.dr.sc. Ljiljana Perić, dr.med., prof.dr.sc. Biserka Trošelj Vukić, dr.med., doc.dr.sc. Dragan Ledina, dr.med., izv.prof.dr.sc. Ivan Puljiz, dr.med., izv.prof. dr.sc. Davorka Lukas, dr.med., doc.dr.sc. Dragan Lepur, dr.med., prim.dr.sc. Srđan Roglić, dr.med., doc.dr.sc. Miroslav Mayer, dr.med., prim.dr.sc. Darko Richter, dr.med., prim.dr.sc. Marinko Vučić, dr. med., doc.dr.sc. Edvard Galić, dr.med. i prim.dr.sc. Marinko Artuković, dr.med.

Povjerenstvo je dana 8. rujna 2020. godine usvojilo Smjernice za liječenje oboljelih od COVID-19, verzija 1, koje su upućene svim zdravstvenim ustanovama u Republici Hrvatskoj u kojima se liječe bolesnici oboljeli od COVID-19 infekcije. Na sjednici Povjerenstva održanoj 19. studenoga 2020. godine prihvaćene su izmjene i dopune navedenih Smjernica pod nazivom Smjernice za liječenje oboljelih od koronavirusne bolesti 2019 (COVID-19) verzija 2, kojih su se obvezni pridržavati svi zdravstveni radnici u Republici Hrvatskoj.

Nove smjernice su dostupne na poveznici.

Fighting COVID-19 with water

Gordan Lauc[1], Alemka Markotić[2], Ivan Gornik[3], Dragan Primorac[4-9]

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[2] Clinics for Infective Diseases, Dr. Fran Mihaljević, Zagreb, Croatia
[3] Department of Emergency Medicine, Clinical Hospital Zagreb, Zagreb, Croatia
[4] St Catharine Hospital, Zagreb, Croatia
[5] Eberly College of Science, Penn State University, USA
[6] University of Split School of Medicine, Split, Croatia
[7] University of Osijek School of Medicine, Osijek, Croatia
[8] University of Osijek Faculty of Dental Medicine and Health, Croatia
[9] Medical School REGIOMED, Coburg, Germany

Mucins mimic cell surface glycosylation and by acting as a decoy trap viral particles, which are then transported out of airways by mucociliary clearance.

Recent epidemiological data from several sources show that transmission of coronavirus disease (COVID-19) is more efficient in cold and dry climate than in warm and humid locations [1,2]. Strong seasonal character of most respiratory viruses also suggests the important role of environment for viral transmission [3]. This is most often interpreted by seasonal indoor crowding and effects of temperature and humidity on stability of viral particles, but we suggest that this effect is by large a consequence of inactivation of the mucosal barrier by dry air in heated indoor spaces.

Inter-individual differences within the human population are glycan-based in a substantial part and glycan diversity represent one of the main defenses of all higher organisms against pathogens. Glycans (which are covalently attached to most proteins) are chemical structures that are being inherited as complex traits, which enables diversity and results in significant inter-individual variation in glycome composition [4]. Most interactions between humans and pathogens involve glycans, and diversity in the thick glycocalyx layer that covers the cell membrane provides us with the important "herd innate protection" [5]. Additional layer of protection is provided by mucins, a group of highly glycosylated proteins that are secreted onto our mucosal barriers. Mucins mimic cell surface glycosylation and by acting as a decoy trap viral particles, which are then transported out of airways by mucociliary clearance [6].

However, for this barrier to stay functional it is necessary to stay well hydrated to both maintain its structural integrity and enable constant flow of mucins that carry viruses and other pathogens out of the airways [6]. If exposed to dry air, these barriers dry out and cannot perform their protective functions [7]. This promotes both initial infection and expansion of viruses along the airways [8]. Animal experiments convincingly demonstrated that increasing relative humidity from 20% to 50% can significantly decrease mortality from influenza infections [8]. The Yale research team confirmed that low humidity influences immune response. It does so through preventing cilia from removing viral particles and mucus, reducing ability of airway cells to repair mutilation caused by virus in the lung and failing to alert neighbouring cells by virus-infected cells via interferons to the viral threat [8].

Air in most heated residential and commercial buildings is very dry, which inactivates mucosal barrier and promotes viral transmission.

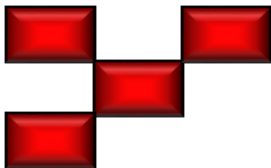
Cijepljenje

On 26 October 2020, ECDC published a report on Key aspects regarding the introduction and prioritisation of COVID-19 vaccination in the EU/EEA and the UK.

On 2 December 2020, ECDC published an overview of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA and the UK.

On 22 December 2020, ECDC published a new overview of COVID-19 vaccination and prioritisation strategies in the EU/EEA.

On 1 February 2021, ECDC published an updated overview of the implementation of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA.



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COVID-19 VACCINE TRACKER

110
VACCINE CANDIDATES

312
TRIALS

14
APPROVED VACCINES

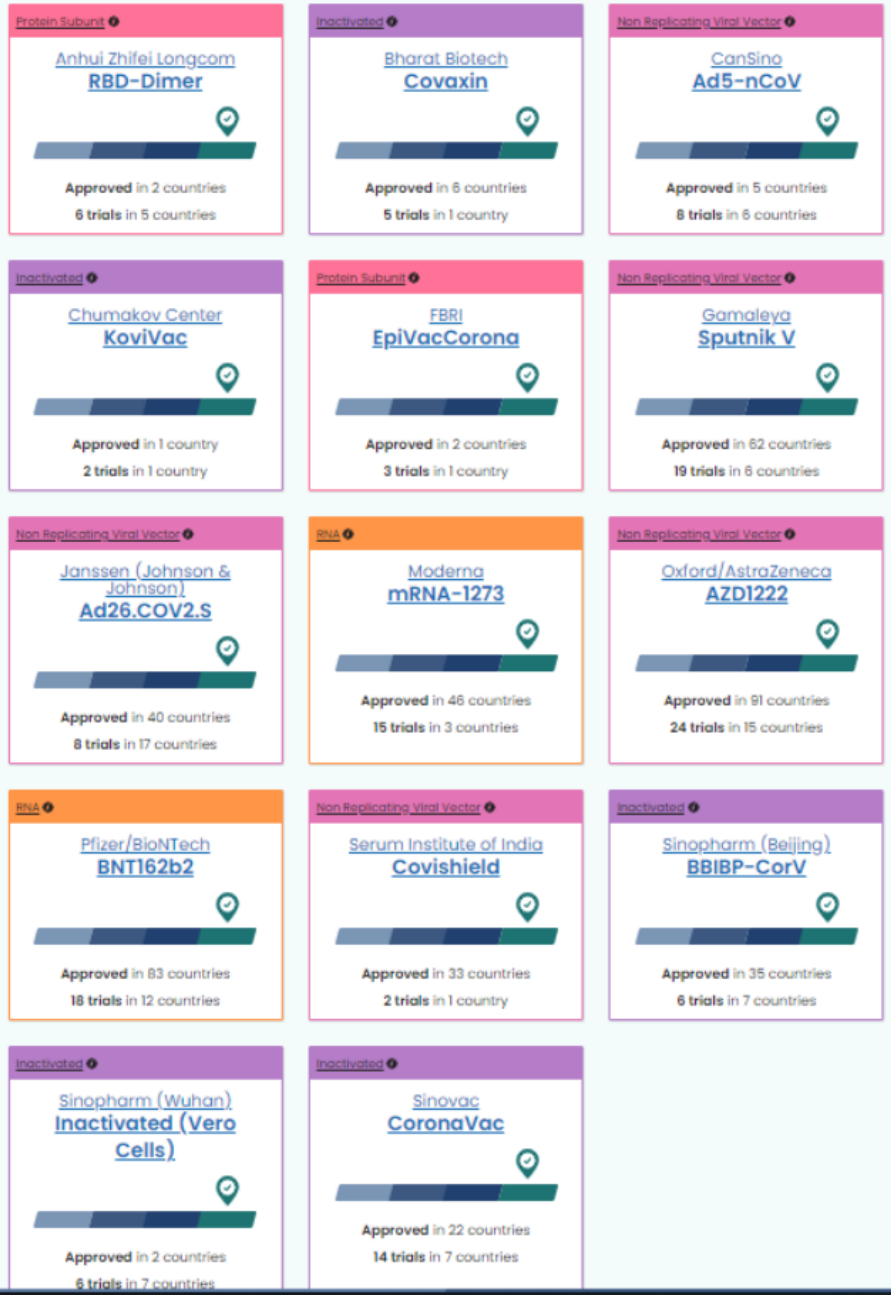
About Trial Phases

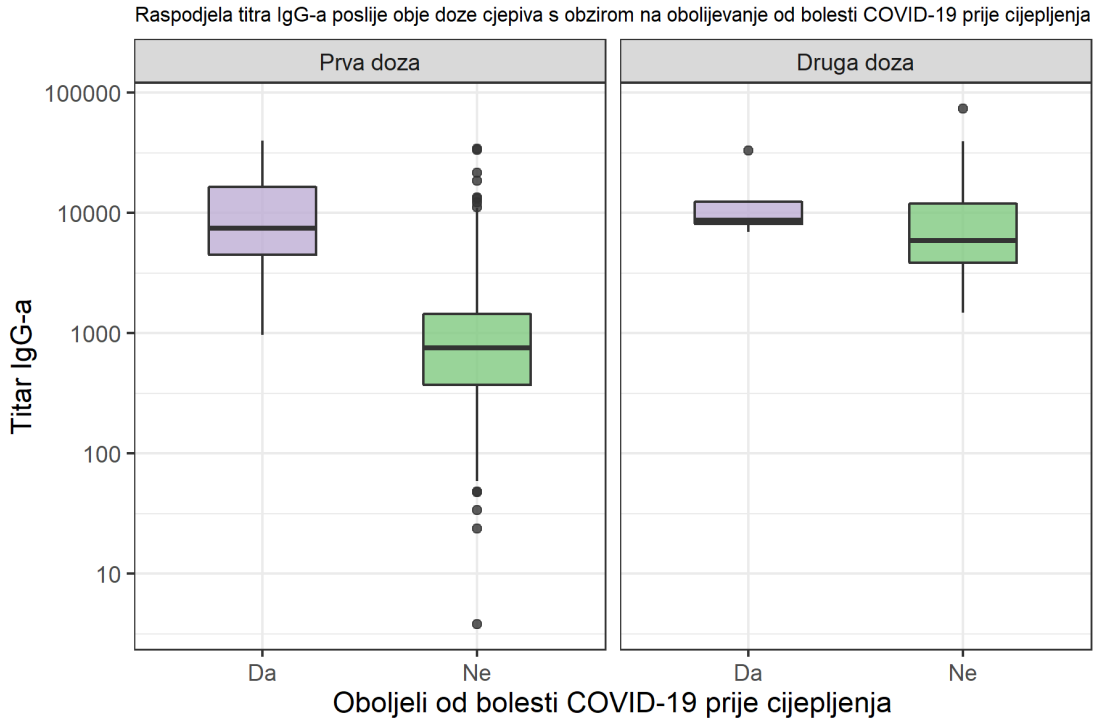
Last Updated 21 April 2021.

14 Vaccines Approved by at Least One Country

Last Updated 21 April 2021.

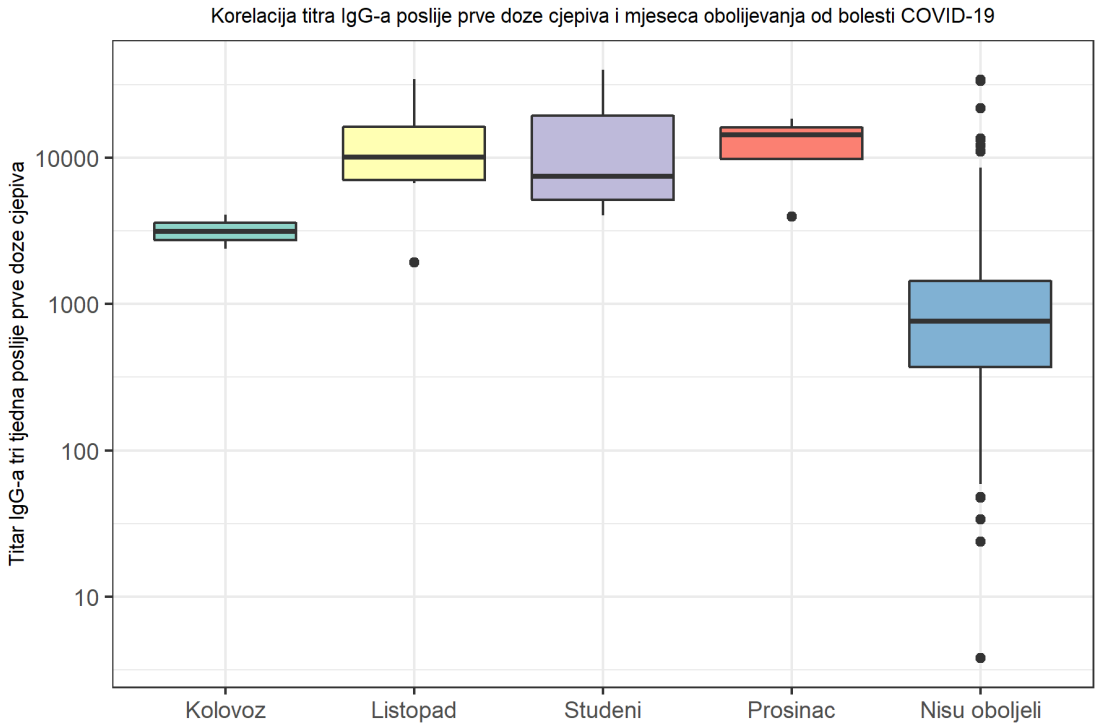
14 Vaccines Approved by at Least One Country





Slika 11. Raspodjela titra IgG-a poslije obje doze cjepiva s obzirom na obolijevanje od bolesti COVID-19 prije cijepljenja (prva doza – statistički značajna razlika u medijanima, p = 0.000).

Đaković Rode O i sur. Neobjavljeni podaci



Slika 12. Korelacija titra IgG-a tri tjedna poslije prve doze cjepiva i mjeseca obolijevanja od bolesti COVID-19.

Đaković Rode O i sur. Neobjavljeni podaci

Hvala na pozornosti