

Stvaranje preduvjeta za prikupljanje COVID-19 konvalescentne plazme u Hrvatskom zavodu za transfuzijsku medicinu

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M.¹, Topić Šestan P.¹, Vuk T.¹, Jukić I.¹*

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Epidemija COVID-19 prvi je put identificirana u Wuhanu i čini se da je povezana s veleprodajnom tržnicom morskih plodova Huanan.

Trenutno ostaje nekoliko pitanja u vezi s podrijetlom

1. Uzročnik, SARS-CoV-2, usko je povezan s koronavirusom **šišmiša** (RaTG13), iako je njegova domena za vezanje receptora sličnija onoj kod koronavirusa **ljuskavaca** (pangolina).
 2. iako se naširoko predlagalo da je tržnica Huanan izvorno mjesto izbijanja SARS-CoV-2, značajan broj početnih slučajeva nije se mogao povezati s tm izvorom.
- To dovodi u sumnju ideju o jedinstvenom događaju prelijevanja zoonoza na ljude u početnoj epidemiji.



11.ožujak 2020.



World Health
Organization

– proglašena pandemija



REPUBLIKA HRVATSKA
MINISTARSTVO ZDRAVSTVA

KLASA: 011-02/20-01/143
URBROJ: 534-02-01-2/6-20-01
Zagreb, 11. ožujka 2020.

Na temelju članka 2. stavka 4. Zakona o zaštiti pučanstva od zaraznih bolesti („Narodne novine“, br. 79/07, 113/08, 43/09, 130/17 i 114/18) i članka 197. Zakona o zdravstvenoj zaštiti („Narodne novine“, br. 100/18 i 125/19), a na prijedlog Hrvatskog zavoda za javno zdravstvo, ministar zdravstva donosi

ODLUKU

o proglašenju epidemije bolesti COVID-19 uzrokovana virusom SARS-CoV-2

I.

Ovom Odlukom proglašava se epidemija bolesti COVID-19 uzrokovana virusom SARS-CoV-2 na području čitave Republike Hrvatske.

II.

Ova Odluka stupa na snagu danom donošenja.



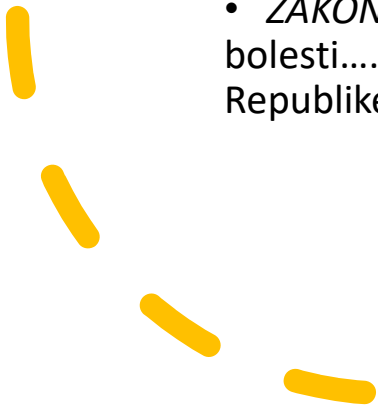


Što to znači?

1. Da se radi o izvanrednoj situaciji u javnom zdravstvu koja ima značajan potencijal utjecati na nacionalnu sigurnost ili zdravlje i sigurnost građana u RH

2. Da postoje okolnosti koje opravdavaju odobrenje hitne uporabe lijekova i bioloških proizvoda tijekom pandemije

- *ZAKON O ZAŠTITI PUČANSTVA OD ZARAZNIH BOLESTI*: u slučaju proglašenja epidemije zarazne bolesti..... Vlada Republike Hrvatske je ovlaštena na prijedlog ministra utvrditi bitan interes Republike Hrvatske za nabavu roba, usluga i radova u cilju sprečavanja i suzbijanja te zarazne bolesti.



Studeni, 2021.



Globally, as of **6:40pm CEST, 27 October 2021**, there have been **244,385,444 confirmed cases** of COVID-19, including **4,961,489 deaths**, reported to WHO. As of **25 October 2021**, a total of **6,697,607,393 vaccine doses** have been administered.

01

Konvalescentna plazma - prvi put u terapiji primijenili Emil von Behring i Shibasaburo Kitasato, 1892. - za liječenje difterije i tetanusa

02

Uspješno se koristila se u nekoliko drugih ozbiljnih zaraznih bolesti, teški akutni respiratorni sindrom (SARS) i bliskoistočni respiratorni sindrom (MERS), influenza H1N1, ptičijia gripa H5N1, H7N9.

03

Izbijanje pandemije COVID-19 uvelike je ubrzalo istraživanje kliničkih ispitivanja koje procjenjuje sigurnost i učinkovitost CP kao hitne terapije.

Uključuje organizaciju
etičkih pitanja kao i
usklađivanje s
regulatornim zahtjevima

Uključuje organizaciju
infrastrukturnih pitanja





REPUBLIKA HRVATSKA
MINISTARSTVO ZDRAVSTVA

KLASA: 023-03/20-01/235
URBROJ: 534-04-3-2/2-20-11
Zagreb, 8. lipnja 2020. godine

REPUBLICA HRVATSKA 251-541 HRVATSKI ZAVOD ZA TRANSFUZIJSKU MEDICINU		
Primljeno:	16-06-2020	
Klasifikacijski oznaka:	I strojstvena jedinica	
023-03/20-01/15	8/11	
Uredbeni broj:	Prihodi	Vrijednost
534-20-20		

Hrvatski zavod za transfuzijsku medicinu
Petrova 3
10 000 Zagreb
n/p doc.dr.sc. Irena Jukić, dr.med.

PREDMET: Proizvodnja svježe zamrznute COVID-19 konvalescentne plazme dobivene aferezom za potrebe transfuzijskog liječenja oboljelih od COVID-19
- suglasnost, dostavlja se

Poštovani,

Ministarstvo zdravstva zaprimilo je Vaš zahtjev za odobrenjem pripremanja svježe zamrznute COVID-19 konvalescentne plazme dobivene postupkom afereze (KLASA: 023-03/20-01/15, URBROJ: 251-541-01/1-20/16), od 24. travnja 2020. godine, te smo na isti zatražili i mišljenje Službe za inspekciju krvi, tkiva i stanica.

Nastavno na zaprimljeno inspeksijsko mišljenje (KLASA: 543-02/20-13/01, URBROJ: 534-09-3/1-20-2) od 7. svibnja 2020. godine i dostavljene otklonjene nesukladnosti od strane Vaše ustanove (KLASA: 023-03/20-01/235, URBROJ: 381-20-10) od 18. svibnja 2020. godine, obavještavam Vas kako je Ministarstvo zdravstva suglasno da Vaša ustanova započne sa postupcima za pripremanje svježe zamrznute COVID-19 konvalescentne plazma osoba koje su preboljele COVID-19 za potrebe transfuzijskog liječenja oboljelih od COVID-19.

S poštovanjem,



Na znanje:

Klinika za infektivne bolesti „dr. Fran Mihaljević“



Ksaver 200a, 10 000 Zagreb, Republika Hrvatska, T +385 1 46 07 555, F +385 1 46 77 076



HRVATSKI ZAVOD ZA
TRANSFUZIJSKU MEDICINU
ZAGREB, Petrova 3
Etičko povjerenstvo
KLASA: 003-06/20-04/02
URBROJ: 251-541-06/6-20-2
U Zagrebu, 07. svibnja 2020.

Raspravljajući o zahtjevu doc.prim.dr.sc. Irene Jukić, dr.med., Etičko povjerenstvo Hrvatskog zavoda za transfuzijsku medicinu na sastanku održanom elektroničkim putem donijelo je sljedeće:

MIŠLJENJE

Udovoljava se pisanom zahtjevu doc.prim.dr.sc. Irene Jukić, dr. med. te odobrava prikupljanje konvalescentne plazme COVID-19 postupkom afereze od osoba koje su preboljele infekciju uzrokovanu SARS-Cov-2 virusom. Konvalescentna COVID-19 plazma izdavalna bi se na zahtjev kliničara u strogoj indikaciji za liječenje COVID-19 te na zahtjev Centra za istraživanje i prijenos znanja u biotehnologiji Sveučilišta u Zagrebu u svrhu proizvodnje specifičnih imunoglobulina.

Svi prikupljeni podaci o osobama koje su se oporavile od COVID-19 i pristupile darivanju konvalescentne plazme bili bi trajno pohranjeni i zaštićeni od neovlaštenog uvida.

Davatelji konvalescentne plazme će biti upoznati s cjelokupnim postupkom i svrhom prikupljanja konvalescentne COVID-19 plazme, što bi potvrdili potpisanim informativnim pristankom.

Etičko povjerenstvo:

Jagrij Sandra Jagrić, dr.med., spec.transfuziolog,
Tom Prim.dr.sc. Tomislav Vuk, dr.med., spec.transfuziolog,
Patricija Patricija Topić Šestan, dr.med., spec.transfuziolog
Mušlin Tatjana Mušlin, dr.med.,
Jadro Marko Jadro, mag.oec.

Odobrenje Ministarstva RH
Odobrenje Etičkog povjerenstva
HZTM

1. dostupnost populacije darivatelja koji su se oporavili od bolesti i mogu donirati konvalescentnu plazmu

2. banka krvi

3. dostupnost testova, uključujući testove za mjerenje neutralizacije virusa i serološke testove

4. laboratorijsku podršku za provođenje ovih testova, BSL3

5. usklađenost s propisima, uključujući odobrenje institucionalnog

6. u idealnom slučaju, upotreba konvalescentne plazme uključivala bi više centara, slijedila bi randomizirane kontrolne protokole i imala bi jedan centar kao upravno tijelo

**1. „Upravljanje zaraznim bolestima uzrokovanim
koronavirusima te društvenim i obrazovnim aspektima
pandemije”**

(IP-CORONA-2020-04)

„Development of premises for implementation of SARSCoV-
2 serotherapy in Croatia“ (IP CORONA-2020-04-2053)

- Lipanj 2020.



**2. Increasing EU capacity for Covid-19 Convalescent
Plasma Collection**

- Lipanj 2020.

Agreement number PPPA-ECI-CCP-2020

Mono beneficiary model  Ref. Ares(2020)7333419 - 04/
grant agreement: August 2019



EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY
Health Systems, medical products and innovation

GRANT AGREEMENT FOR AN ACTION
UNDER EMERGENCY SUPPORT INSTRUMENT (ESI)
AGREEMENT NUMBER — PPPA-ECI-CCP-2020 – SI2.839205



Brussels,
SANTÉ B4/DF/

An EU programme of COVID-19 convalescent plasma collection and transfusion

Guidance on collection, testing, processing, storage, distribution and monitored use

This document has been endorsed by the Competent Authorities for Substance of Human Origin Expert Group (CASoHO E01718) following consultation of the competent authorities for blood and blood components and by the European Centre for Disease Prevention and Control. While this document is not legally binding, it aims to facilitate a common approach across EU Member States to the donation, collection, testing, processing, storage, distribution and monitoring of convalescent plasma for the treatment of Covid-19. This document is without prejudice to the requirements of the Union blood legislation, any more stringent national measures in place at Member State level and national requirements on the use of this treatment, all of which continue to apply. This guidance will be updated as needed, in line with scientific developments.

Version 1.0 April 4 2020

Background

Plasma collected from patients that have recovered from an infectious disease has been used over many decades for a variety of different infectious agents¹, although evidence of its effectiveness and safety is mostly limited to empirical reports. Referred to as convalescent plasma, it can be transfused to patients fighting an infection or can be used to manufacture immune globulin concentrates (plasma derived medicinal products). During a rapidly expanding outbreak of a viral infection, large populations of susceptible persons may become ill early in the event, prior to availability of effective vaccines and antiviral therapies. As highlighted by the WHO Blood Regulators Network¹, an organised programme to collect convalescent plasma or serum from disease survivors could provide a potentially valuable empirical intervention while data on effectiveness and safety of its use are being gathered through structured clinical trials.

The COVID-19 pandemic is a clear situation where plasma from recovered patients might be a valuable resource to support the disease treatment within randomised or case-control clinical trials or observational studies of plasma transfusion and in the development of a plasma-derived



COMMENT | VOLUME 20, ISSUE 4, P398-400, APRIL 01, 2020

Convalescent plasma as a potential therapy for COVID-19

Long Chen · Jing Xiong · Lei Bao · Yuan Shi

Published: February 27, 2020 · DOI: [https://doi.org/10.1016/S1473-3099\(20\)30141-9](https://doi.org/10.1016/S1473-3099(20)30141-9)

References

Article Info

Linked Articles

Related

Specialty

Collections

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), 2020, this virus has affected more than 77 700 people worldwide and ca treatment has been proven to be effective for SARS-CoV-2 infection. Apart f and extracorporeal membrane oxygenation for the critically ill patients, sp the USA, the first patient infected with SARS-CoV-2 was treated by supporti recovered and was discharged.¹ However, randomised clinical trials are ne the treatment of COVID-19.

Convalescent plasma or immunoglobulins have been used as a last resort

JCI The Journal of Clinical Investigation

The convalescent sera option for containing COVID-19

Arturo Casadevall, Liise-anne Pirofski

13. Ožujak 2020.

J Clin Invest. 2020;130(4):1545-1548. <https://doi.org/10.1172/JCI138003>.

Viewpoint COVID-19

As of early 2020, humanity is confronting a pandemic in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 causes coronavirus disease, abbreviated as COVID-19. At the time of this writing, SARS-CoV-2 is spreading in multiple countries, threatening a pandemic that will affect billions of people. This virus appears to be a new human pathogen. Currently there are no vaccines, monoclonal antibodies (mAbs), or drugs available for SARS-CoV-2, although many are in rapid development and some may be available in a short time. This Viewpoint argues that human convalescent serum is an option for prevention and treatment of COVID-19 disease that could be rapidly available when there are sufficient numbers of people who have recovered and can donate immunoglobulin-containing serum. Passive antibody therapy Passive antibody therapy involves the administration of antibodies against a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease due to that agent. In contrast, active vaccination requires the induction of an immune response that takes time to develop and varies depending on the vaccine recipient. Thus, passive antibody administration is the only means of providing immediate immunity to susceptible persons. Passive antibody therapy has a storied history going back to the 1890s and was the only means of treating certain infectious diseases prior to the development of antimicrobial therapy in [...]

15.0žujak 2020.

Effectiveness of convalescent plasma therapy in severe COVID-19 patients

Kai Duan^{a,b,1}, Bende Liu^{c,1}, Cesheng Li^{d,1}, HuaJun Zhang^{a,1}, Ting Yu^{e,1}, Jieming Qu^{a,h,1}, Min Zhou^{a,h,1}, Jianhong Yu^d, Li Chen¹, Shengli Meng^b, Yong Hu¹, Cheng Peng^a, Mingchao Yuan^a, Jinyan Huang^g, Zejun Wang^g, Wei Chen^a, Xiaoxiao Gao^a, Dan Wang^b, Xiaoqi Yu^m, Li Li^b, JiaYou Zhang^g, Xiao Wu^d, Bei Li^f, Yanping Xu^{a,h}, Yue Wang^g, Yan Peng^d, Yeqin Hu^b, Lianzhen Lin^d, Xuefei Liu^{a,h}, Shihe Huang^g, Zhijun Zhou^g, Lianghao Zhang^g, Yue Wang^g, Zhi Zhang^g, Kun Deng^g, Zhiwu Xia^b, Qin Gong^g, Wei Zhang^g, Xiaobei Zheng^g, Ying Liu^g, Huichuan Yang^g, Dongbo Zhou^g, Ding Yu^a, Jifeng Houⁿ, Zhengli Shi^o, Saijun Chen¹, Zhu Chen¹, XinXin Zhang¹, and Xiaoming Yang^{b,2}

^aChina National Biotech Group Company Limited, 100029 Beijing, China; ^bNational Engineering Technology Research Center for Combined Vaccines, Wuhan Institute of Biological Products Co., Ltd., 430207 Wuhan, China; ^cFirst People's Hospital of Jiangxia District, 430200 Wuhan, China; ^dSinopharm Wuhan Plasma-derived Biotherapies Co., Ltd., 430207 Wuhan, China; ^eKey Laboratory of Special Pathogens, Wuhan Institute of Virology, Center for Biosafety and Mega-Science, Chinese Academy of Sciences, 430071 Wuhan, China; ^fWuhan Jinyintan Hospital, 430023 Wuhan, China; ^gDepartment of Respiratory and Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 200025 Shanghai, China; ^hNational Research Center for Translational Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 200025 Shanghai, China; ⁱInstitute of Gastroenterology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 200025 Shanghai, China; ^jClinical Research Center, Department of Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 200025 Shanghai, China; ^kWuhan Blood Bank, Wuhan Institute of Virology, Center for Biosafety and Mega-Science, Chinese Academy of Sciences, 430071 Wuhan, China; ^lDepartment of Hematology, National Research Center for Translational Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 200025 Shanghai, China; ^mResearch Laboratory of Clinical Virology, Ruijin Hospital and Ruijin Hospital North, National Laboratory of Medical Genomics, Shanghai Institute of Hematology, National Research Center for Translational Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 200025 Shanghai, China; ⁿResearch Laboratory of Clinical Virology, Ruijin Hospital and Ruijin Hospital North, National Laboratory of Medical Genomics, Shanghai Institute of Hematology, National Research Center for Translational Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 200025 Shanghai, China; ^oNational Institute for Food and Drug Control of China, 102629 Beijing, China

UNESCO

FULL TEXT LINKS

WILEY Full Text Article

Case Reports | J Med Virol. 2020 Oct;92(10):1890-1901. doi: 10.1002/jmv.25882.
Epub 2020 Jun 29.

Treatment with convalescent plasma for COVID-19 patients in Wuhan, China

Mingxiang Ye^{1,2}, Dian Fu^{2,3}, Yi Ren^{2,4}, Faxiang Wang^{2,5}, Dong Wang^{1,2}, Fang Zhang^{1,2}, Xinyi Xia^{6,7}, Tangfeng Lv^{1,2}

Affiliations
PMID: 32293713 | PMCID: PMC7262027 | DOI: 10.1002/jmv.25882

Free PMC article

JAMA FULL TEXT ARTICLE

Randomized Controlled Trial | JAMA. 2020 Aug 4;324(5):460-470. doi: 10.1001/jama.2020.10044.

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial

Ling Li^{1,2}, Wei Zhang^{3,4}, Yu Hu⁵, Xunliang Tong⁶, Shangen Zheng⁷, Juntao Yang⁸, Yujie Kong^{1,2}, Lili Ren^{9,10}, Qing Wei¹¹, Heng Mei⁵, Caiying Hu¹², Cuihua Tao^{13,14}, Ru Yang¹⁵, Jue Wang^{1,2}, Yongpei Yu¹⁶, Yong Guo¹⁷, Xiaoxiong Wu¹⁸, Zhihua Xu^{12,19}, Li Zeng^{3,20}, Nian Xiong^{12,21}, Lifeng Chen²², Juan Wang¹¹, Ning Man²³, Yu Liu¹, Haixia Xu^{1,2}, E Deng¹, Xuejun Zhang¹, Chenyue Li^{1,2}, Conghui Wang⁹, Shisheng Su¹⁷, Linqi Zhang²⁴, Jianwei Wang^{9,10}, Yanyun Wu²⁵, Zhong Liu^{1,2}

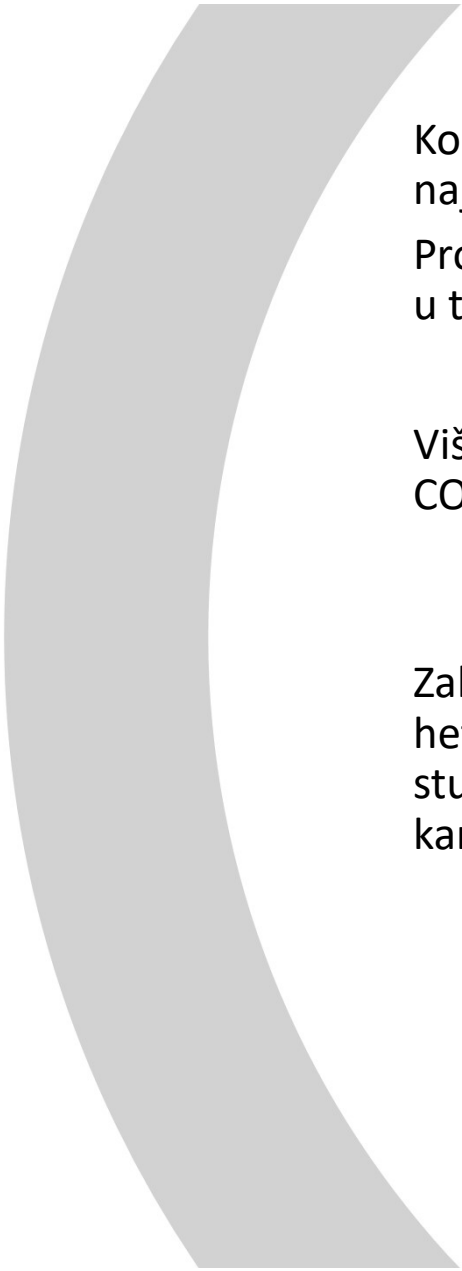
Affiliations
PMID: 32492084 | PMCID: PMC7270883 | DOI: 10.1001/jama.2020.10044

Research

JAMA | Preliminary Communication

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma

Chengguang Shen, PhD; Zhaoqin Wang, PhD; Fang Zhao, PhD; Yang Yang, MD; Jimou Li, MD; Jing Yuan, MD; Fuxiang Wang, MD; Delin Li, PhD; Minghui Yang, PhD; Li Xing, MM; Jinli Wei, MM; Haixia Xiao, PhD; Yan Yang, MM; Jixun Qu, MD; Ling Qing, MM; Li Chen, MD; Zhixiang Xu, MM; Ling Peng, MM; Yanjie Li, MM; Haixia Zheng, MM; Feng Chen, MM; Kun Huang, MM; Yujing Jiang, MM; Dongjing Liu, MD; Zheng Zhang, MD; Yingxia Liu, MD; Lei Liu, MD



Konvalescentna plazma danas je među najproučavanijim i najkorištenijim terapijama protiv COVID-19.

Provedeno je niz objavljenih kao i kliničkih ispitivanja koja su u tijeku kako bi se procijenila njezina učinkovitost i sigurnost.

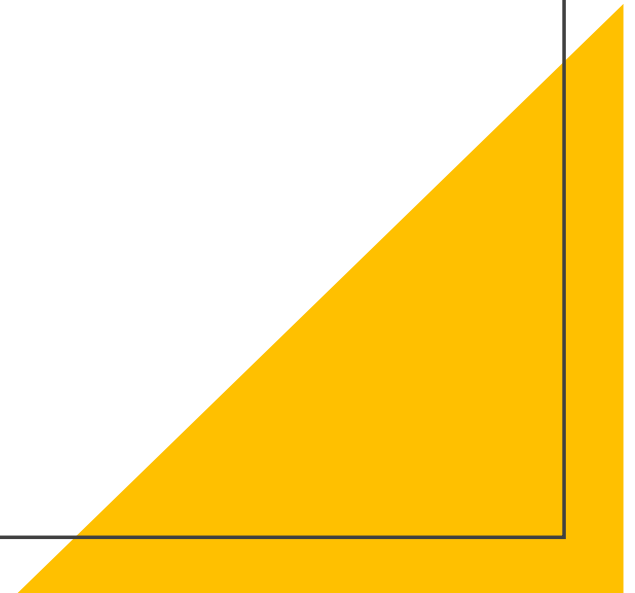
Više od 140 kliničkih ispitivanja koji posebno procjenjuju CP u COVID-19 registrirani su do danas širom svijeta

Zaključci su, međutim, prilično oprečni i odražavaju široku heterogenost između različitih studija u smislu dizajna studije, CP proizvoda i primjene, karakteristika bolesti karakteristika bolesnika.

Čini se da je to tipično za izvanredne situacije.



- Ogromne količine dostupnih kliničkih podataka - u posljednjih godinu dana objavljeno je nekoliko sustavnih pregleda (SR) i metaanaliza kako bi se uskladili rezultati primarnih kliničkih ispitivanja.
- Čak su i sustavni pregledi i meta-analize dali heterogene rezultate.
- Pregled postojećih SR-a - krovni pregled.





March 9, 2021

Nikki Bratcher-Bowman
Acting Assistant Secretary for Preparedness and Response
Office of the Assistant Secretary for Preparedness and Response
Office of the Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Ms. Bratcher-Bowman:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19 (the virus was later named SARS-CoV-2).¹ On March 27, 2020, on the basis of such determination, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act, subject to the terms of any authorization issued under that section.²

On August 23, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with Coronavirus Disease 2019 (COVID-19), pursuant to Section 564 of the Act.³ Subsequently, FDA reissued the Letter of Authorization to add tests acceptable to be used in the manufacture of COVID-19 convalescent plasma, the names and dates of each test are currently listed in Appendix A.⁴

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized high titer COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19, early in the course of disease, and those hospitalized with impaired humoral immunity. The emergency use of the authorized high titer COVID-19

convalescent plasma under this EUA must be consistent with, and may not exceed, the terms of this letter, including the scope and the conditions of authorization set forth below.



EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Ref. Ares(2021)1739358 - 10/03/2021

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety, innovation

Brussels,
SANTÉ B4/DF/

An EU programme of COVID-19 convalescent plasma collection and transfusion

Guidance on collection, testing, processing, storage, distribution and monitored use

This document has been endorsed by the Competent Authorities for Substance of Human Origin Expert Group (CASoHO E01718) following consultation of the competent authorities for blood and blood components and by the European Centre for Disease Prevention and Control. While this document is not legally binding, it aims to facilitate a common approach across EU Member States to the donation, collection, testing, processing, storage, distribution and monitoring of convalescent plasma for the treatment of COVID-19 (CCP). This document is without prejudice to the requirements of the Union blood legislation, any more stringent national measures in place at Member State level and national requirements on the use of this treatment, all of which continue to apply. This guidance is updated as needed, in line with scientific developments. 10 March 2021
Version 4.0

Distribution of COVID-19 convalescent plasma

Convalescent plasma should be distributed by blood establishments on the request of a hospital in the following circumstances:

- the specific patient has laboratory confirmed COVID-19 and is in the early or moderate clinical stage of disease (WHO classification) or has impaired humoral immunity;
- CCP should be applied to these patients as early as possible, ideally within 3 days of symptom onset or as early as possible after hospital admission;
- the patient has been hospitalised, unless the plasma is supplied in the context of a clinical trial on early transfusion of non-hospitalised patients;
- the patient, or their legal representative, has given informed consent to transfusion with COVID-19 convalescent plasma.

The uncertainty about the efficacy of convalescent plasma in treating patients with COVID-19 should be communicated to potential recipients or their legal representatives, whether they are part of a clinical trial or of monitored use, to avoid fostering unfounded expectations and to ensure that prospective recipients or their legal representatives make informed decisions regarding treatment.

Blood services should aim to issue the components with the highest antibody titres available, while respecting the treatment and clinical trial protocols in place locally. An evidence-base for a minimal titre of neutralising antibodies with significant clinical efficacy of convalescent is limited. The US data described above, together with initial research [5, 6], suggests that a titre of $\geq 1:160$ might be an appropriate threshold to apply but a definitive threshold is yet to be established in clinical trials. There is no international standardized unit for "titre" nor is there currently any calibration possible to reliably compare titres among unrelated studies. Therefore, each CCP programme should specify its threshold titre of neutralizing antibodies to allow for a correlation of antibody titre and patient outcome. Only CCP with high neutralising antibody titres should be used in the treatment of COVID-19 patients¹. A suggested dose of high titre convalescent plasma is one unit; for low titre plasma, two units of convalescent plasma might be transfused. If two units are to be transfused they should be from different donors.

Odabir davatelja

- davatelji konvalescentne plazme moraju zadovoljiti kriterije za odabir dobrovoljnih davatelja krvi i krvnih sastojaka na staničnom separatoru
- osobe koje su primile cjepivo protiv COVID-19 i nisu preboljele COVID-19 **NE mogu** darivati konvalescentnu plazmu.
- prethodna dijagnoza COVID-19, potvrđena pozitivnim RT-PCR testom, SARS-CoV-2 antigenskim testom ili testom na SARS-CoV-2 protutijela, bez obzira na prisutnost simptoma.
- pojedinci koji su imali tipične simptome COVID-19, ali bolest nije potvrđena niti jednim od testova također mogu pristupiti darivanju, o čemu odlučuje liječnik na pregledu DDK, uzimajući u obzir anamnestičke i epidemiološke podatke.
- **28 dana od prestanka simptoma bolesti COVID-19**
- ukoliko je osoba bila asimptomatska, a laboratorijski joj je potvrđena infekcija SARS-CoV-2, period odgode od 28 dana počinje teći od datuma uzimanja uzorka za testiranje na SARS-CoV-2.
- preboljenje COVID-19 unutar posljednja **4 mjeseca ako nisu cijepljeni**; ukoliko su preboljeli i cijepljeni, **nema vremenskog ograničenja**
- davatelji konvalescentne plazme, koji su tijekom liječenja bolesti COVID-19 primili konvalescentnu plazmu, moraju ispunjavati sve kriterije za darivanje pune krvi i koncentrata trombocita (KT), uključujući odgodu od 4 mjeseca od datuma transfuzije (primanja transfuzije konvalescentne plazme).
- **osobe koje su preboljele COVID-19, a primile su i cjepivo protiv COVID-19 mogu darivati konvalescentnu plazmu (uz važeću odgodu, ovisno o vrsti cjepiva).**
- darivatelju koji je u prvoj donaciji konvalescentne plazme iz PUK imao zadovoljavajući titar protutijela, može se i u idućoj donaciji također ponoviti postupak uzimanja uzorka za određivanje titra (bez obzira što je prošlo više od 4 mjeseca od preboljenja).
- ukoliko kriteriji zadovoljavaju, tada:
- davateljima kod prvog dolaska uzimaju uzorci za analizu KKS i jetrene funkcije (AST, ALT, ukupni proteini) te prema indikaciji uzorci za ALA/ATA (prethodne transfuzije/trudnoća/pobačaji) – CP afereza
- samo muški DDK –CP iz pune krvi



HRVATSKI LJEČNIČKI ZBOR
Hrvatsko društvo za transfuzijsku medicinu
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OIB60192951611



PREPORUKE HRVATSKOG DRUŠTVA ZA TRANSFUZIJSKU MEDICINU TIJEKOM PANDEMIJE VIRUSA SARS-CoV-2

Peto izdanje

10.06.2021.

Ovaj dokument pruža smjernice o upravljanju opskrbom krvnim pripravcima kao odgovor na pandemiju COVID-19 i smjernice o zaštiti djelatnika u transfuzijskoj djelatnosti. Namijenjen je svim transfuzijskim ustanovama koje su odgovorne za opskrbu krvnim pripravcima kao i bolničkim transfuzijskim jedinicama.

Peto izdanje ovog dokumenta mijenja se izmjenama i dopunama koje su u skladu s novim preporukama u vezi cijepljenja, a odnose se prvenstveno na odgodu darivanja krvi nakon primjene vektorskog cjepiva.

	Vrsta dokumenta: RADNA UPUTA	Izdanje: 06
	Naziv: PRIKUPLJANJE, PROIZVODNJA I SKLADIŠTENJE KONVALESCENTNE COVID-19 PLAZME	Primjena od: 03.05.2021.
	Oznaka: RU-BAK-005	Strana: 1/10

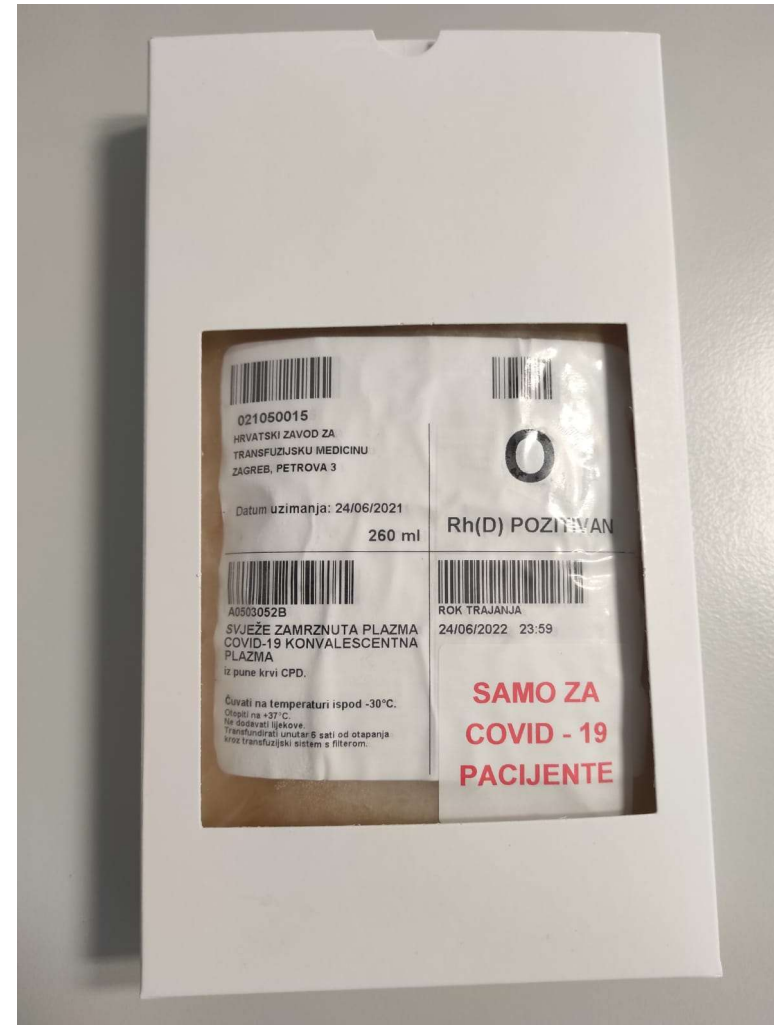
1. SVRHA

Ova radna uputa nastala je kao posljedica zahtjeva POK-07-05 – Dobrovoljni davatelji krvi i POK-04-02 – Banka krvi.

Svrha ove radne upute je propisati prikupljanje, proizvodnju i skladištenje konvalescentne COVID-19 plazme.

Metode

1. Afereza
 2. Puna krv
- Na početku CP su davale oporavljene osobe koje do tada nikada nisu darivale krv.
 - Širenjem zaraze sve je veći broj DDK, koji su preboljeli COVID-19, mogao darivati CP
 - Od 01.svibnja 2021. zbog velikih zahtjeva i potencijalnih problema s zadovoljavanjem potreba korištene su obje metode prikupljanja CP.
 - Sve je veći broj i cijepljenih DDK



Cijepljenje



Advancing Transfusion and
Cellular Therapies Worldwide

Updated Information from FDA on Donation of CCP, Blood Components and HCT/Ps, Including Information on COVID-19 Vaccines, Treatment with CCP or Monoclonals

Updated 04 14 2021



Advancing Transfusion and
Cellular Therapies Worldwide

- o individuals who had a positive diagnostic test for SARS-CoV-2 (e.g., nasopharyngeal swab), but never developed symptoms, refrain from donating at least 14 days after the date of the positive test result,
- o individuals who are tested and found positive for SARS-CoV-2 antibodies, but who did not have prior diagnostic testing and never developed symptoms, can donate without a waiting period and without performing a diagnostic test (e.g., nasopharyngeal swab),
- o individuals who received a nonreplicating, inactivated, or mRNA-based COVID-19 vaccine can donate blood without a waiting period,
- o individuals who received a live-attenuated viral COVID-19 vaccine, refrain from donating blood for a short waiting period (e.g., 14 days) after receipt of the vaccine,
- o individuals who are uncertain about which COVID-19 vaccine was administered, refrain from donating for a short waiting period (e.g., 14 days) if it is possible that the individual received a live-attenuated viral vaccine.

FDA will continue to monitor the situation and issue updated information as it becomes available.



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3. KRITERIJI ZA ODABIR DARIVATELJA PUNE KRVI I KONCENTRATA TROMBOCITA NA STANIČNOM SEPARATORU NAKON CJEPLJENJA PROTIV COVID-19

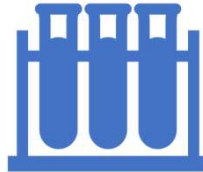
- Ako su cjepiva bazirana na mRNA tehnologiji (Pfizer/BioNTech, Moderna, CureVac) ili ako su bazirana na vektorskoj tehnologiji s nereplikativnim adenovirusom (AstraZeneca/Oxford, Johnson&Johnson/Jansen, Sputnik V):
 - odgoda darivanja za 48 sati nakon cijepljenja zbog moguće pojave lokalnih simptoma na mjestu primjene cjepiva (bol, crvenilo, svrbež, otok).
 - odgoda darivanja za 7 dana od prestanka simptoma u slučaju nuspojava na cjepivo (umor, glavobolja, bolovi u mišićima, zimica, bolovi u zglobovima, povišena tjelesna temperatura, mučnina, limfadenopatija)
- Ako se osoba cijepila atenuiranim cjepivom (kineska cjepiva Sinopharm i Sinovac):
 - odgoda darivanja 14 dana nakon cijepljenja
- Ako osobe ne znaju kojim su cjepivom cijepljene:
 - odgoda darivanja 14 dana nakon cijepljenja

4. KRITERIJI ZA ODABIR DARIVATELJA KONVALESCENTNE PLAZME NAKON CJEPLJENJA PROTIV COVID-19

- Osobe koje su primile cjepivo protiv COVID-19 i nisu preboljele COVID-19 ne mogu darivati konvalescentnu plazmu.
- Osobe koje su preboljele COVID-19, a primile su i cjepivo protiv COVID-19 mogu darivati konvalescentnu plazmu (uz važeću odgodu, ovisno o vrsti cjepiva).
- Darivatelji konvalescentne plazme, koji su tijekom liječenja bolesti COVID-19 primili konvalescentnu plazmu, moraju ispunjavati sve kriterije za darivanje pune krvi i koncentrata trombocita, uključujući odgodu od 4 mjeseca od datuma transfuzije (primanja transfuzije konvalescentne plazme).



Testiranje

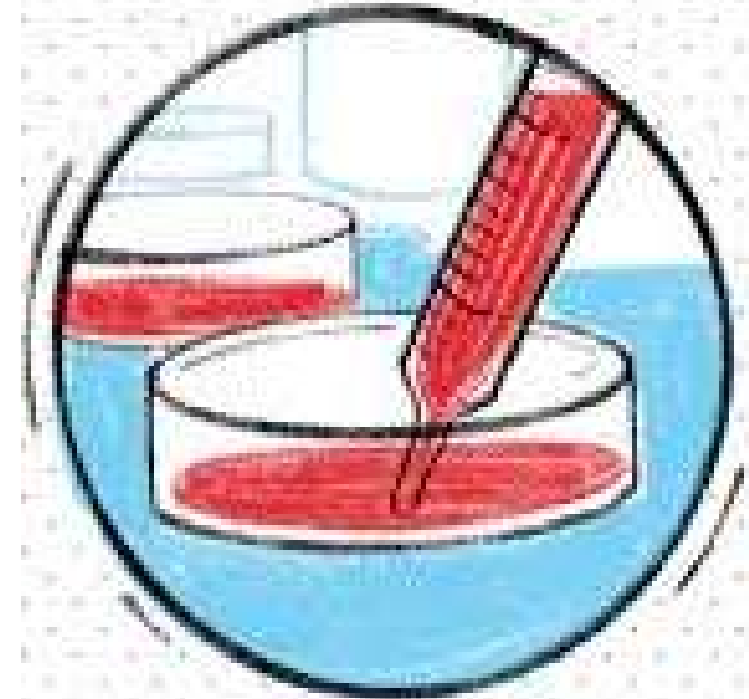


Titre of NAb was measured with the SARS-CoV-2 neutralization assay for quantification of SARS-CoV-2 NAb in BSL3 conditions.

Test has been performed on **Vero E6 cell** suspensions with home working stocks of SARS-CoV-2 virus - clinical isolate of the Laboratory working stock label **SARS-CoV-2 297/20 Zagreb virus**.

Examination of SARS-CoV-2 NAb by neutralization assay is considered the gold standard !!!

- Zbog kompleksnosti testa i čekanja na rezultate rađena je regresijska analiza s dostupnim serološkim testovima.
- Serološki testovi imaju bolju protočnost!
- Različitost izražavanja rezultata – nemoguća usporedba
- Prvi Who Internacionalni standard NIBSC code20/136 za izražavanje rezultata testiranja u IU/ml
- 170 IU/ml



Appendix A: Table of Tests Acceptable for Use in the Manufacture of High Titer COVID-19 Convalescent Plasma

Tests Acceptable for Use in the Manufacture of High Titer COVID-19 Convalescent Plasma			
Manufacturer (listed alphabetically)	Assay	Qualifying Result	Date of Listing under this EUA
Abbott	SARS-CoV-2 IgG (ARCHITECT and Alinity i)	Index (S/C) ≥ 4.5	February 4, 2021
Abbott	AdviseDx SARS-CoV-2 IgG II (ARCHITECT and Alinity i)	≥ 840 AU/mL	March 9, 2021
Beckman Coulter	Access SARS-CoV-2 IgG	S/CO ≥ 3.3	February 4, 2021
EUROIMMUN	Anti-SARS-CoV-2 ELISA (IgG)	Ratio ≥ 3.5	February 4, 2021
GenScript	cPass SARS-CoV-2 Neutralization Antibody Detection Kit	Inhibition ≥ 68%	February 4, 2021
Kantaro	COVID-SeroKlir, Kantaro Semi-Quantitative SARS-CoV-2 IgG Antibody Kit	Spike ELISA > 47 AU/mL	February 4, 2021
Mount Sinai	COVID-19 ELISA IgG	Spike ELISA titer ≥ 1:2880	November 30, 2020
Ortho	VITROS Anti-SARS-CoV-2 IgG	S/C ≥ 9.5	August 23, 2020 ¹¹
Roche	Elecsys Anti-SARS-CoV-2	COI ≥ 109	February 23, 2021
Roche	Elecsys Anti-SARS-CoV-2 S	≥ 132 U/mL	February 4, 2021
Siemens	ADVIA Centaur SARS-CoV-2 IgG (COV2G)	Index ≥ 4.8	February 4, 2021

- Biomerieux Vidas SARS CoV -2 IgG ≥ 10 TV ~ 170IU/ml



WHO International Standard
WHO International Standard for SARS-CoV-2 antibody (human)
NIBSC code: 20/136
Instructions for use
(Version 1.00, Dated)

1. INTENDED USE
The WHO International Standard for anti-SARS-CoV-2 antibody is the freeze-dried equivalent of 0.25 mL of pooled plasma obtained from eleven individuals recovered from SARS-CoV-2 infection. The preparation has been evaluated in a WHO International Collaborative study (1). The intended use of the International Standard is for the calibration and harmonisation of serological assays detecting anti-SARS-CoV-2 neutralising and binding antibody. The material has the same assigned unitage for neutralising and binding antibody. Secondary reagents should be calibrated to the International Standard in the type of assay required. The preparation has been solvent-detergent treated to minimise the risk of the presence of enveloped viruses (2).

2. CAUTION
This preparation is not for administration to humans or animals in the human food chain.

The preparation contains material of human origin, and either the final product or the source materials, from which it is derived, have been tested and found negative for HBsAg, anti-HIV and HCV RNA. As with all materials of biological origin, this preparation should be regarded as potentially hazardous to health. It should be used and discarded according to your own laboratory's safety procedures. Such safety procedures should include the wearing of protective gloves and avoiding the generation of aerosols. Care should be exercised in opening ampoules or vials, to avoid cuts.

3. UNITAGE
The assigned potency of the WHO International Standard for SARS-CoV-2 antibody is 250 IU/ampoule for neutralising activity and 250 IU/ampoule for binding activity. After reconstitution in 0.25 mL of distilled water, the final concentration of the preparation is 1000 IU/mL for neutralising and binding antibody.

8. STABILITY
Reference materials are held at NIBSC within assured, temperature-controlled storage facilities. Reference Materials should be stored on receipt as indicated on the label.

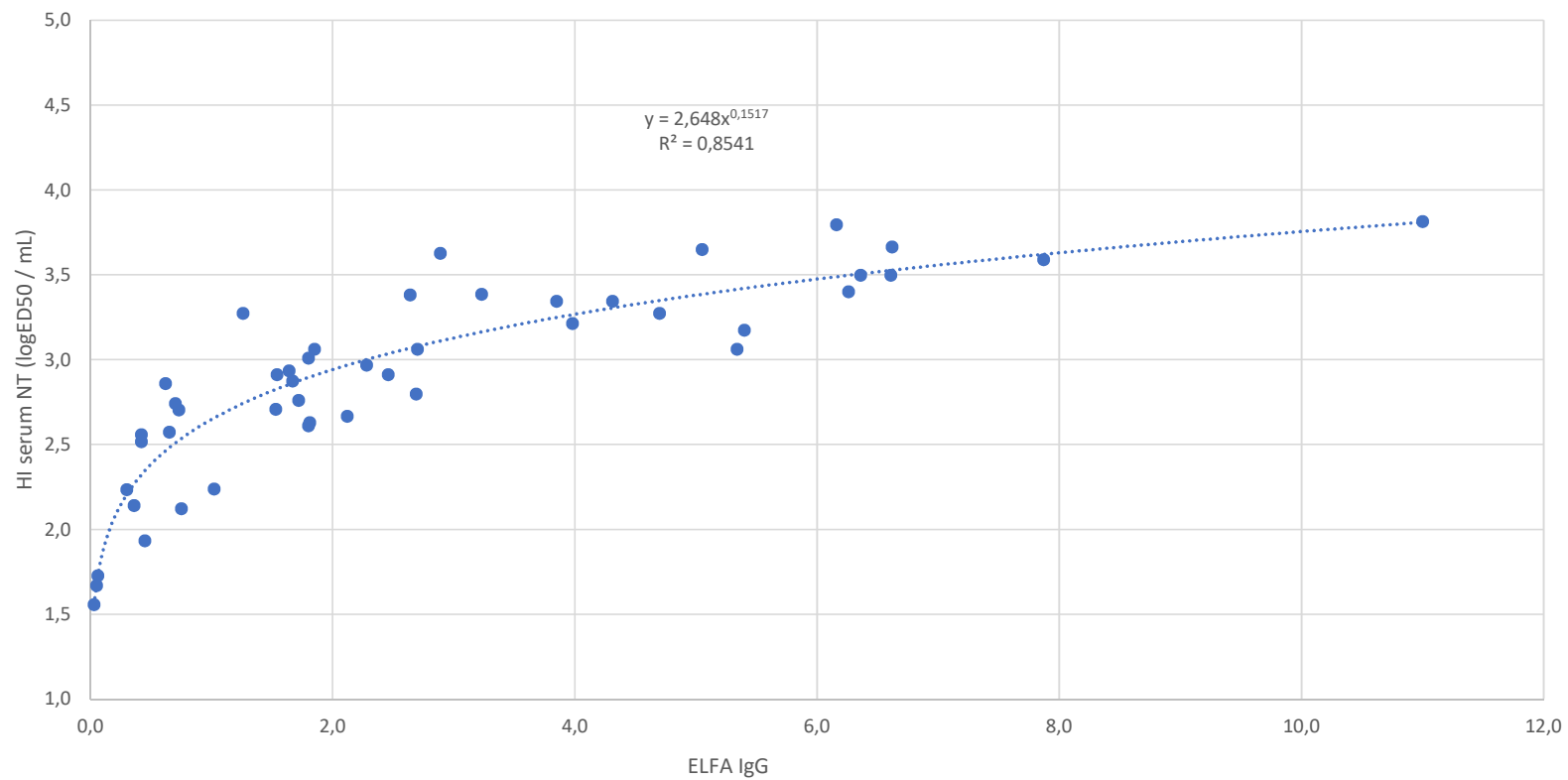
NIBSC follows the policy of WHO with respect to its reference materials.

9. REFERENCES
(1) Mattiuzzo et al. Establishment of the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody, 2020, WHO Expert Committee on Biological Standardization, WHO/BS/2020.xxxx.
(2) Dichtelmüller et al. Robustness of solvent/detergent treatment of plasma derivatives: a data collection from Plasma Protein Therapeutics Association member companies. Transfusion. 2009;49:1931-43.

10. ACKNOWLEDGEMENTS
We would like to wholeheartedly thank the anonymous donors of the plasma samples for their consent which has allowed this material to be prepared; we would like to express our gratitude to those groups and individuals who have coordinated the collection of the convalescent plasma: Malcolm Semple (University of Liverpool, UK), Lance Turtle (University of Liverpool, UK), Peter Openshaw (Imperial College London, UK) and Kenneth Baillie (University of Edinburgh) on behalf of the ISARIC4C Investigators; Heli Harvala Simmonds and David Roberts (National Health Service Blood and Transplant, UK). We would also like to thank NIBSC Standards Production and Development staff for the formulation and distribution of materials. The International Standard for SARS-CoV-2 antibody wouldn't have been possible without the Coalition for Epidemic Preparedness Innovations (CEPI) sponsored the sourcing and formulation of the candidate material.

11. FURTHER INFORMATION
Further information can be obtained as follows:
This material: enquiries@nibsc.org
WHO Biological Standards:
<http://www.who.int/biologicals/en/>
JCTLM Higher order reference materials:
<http://www.bipm.org/en/committees/cj-clim/>

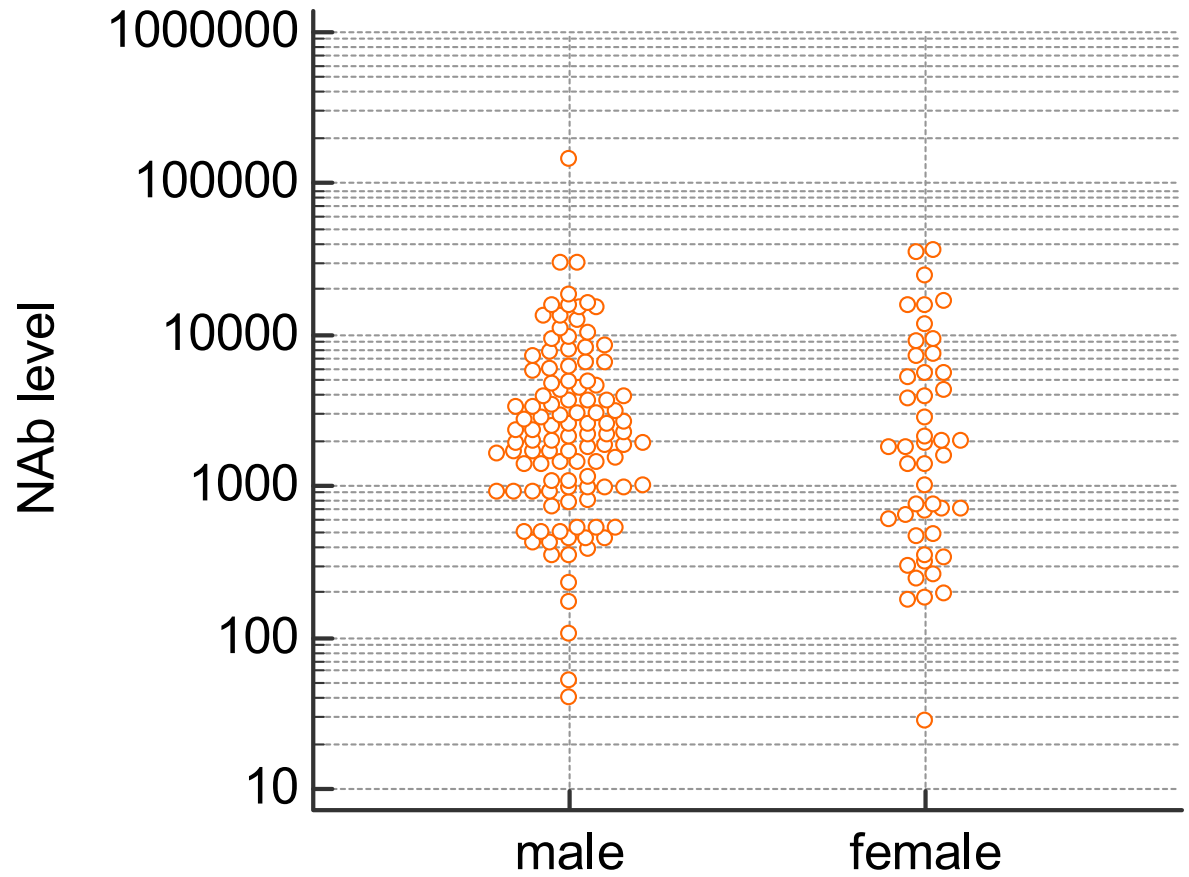
NT versus ELFA IgG

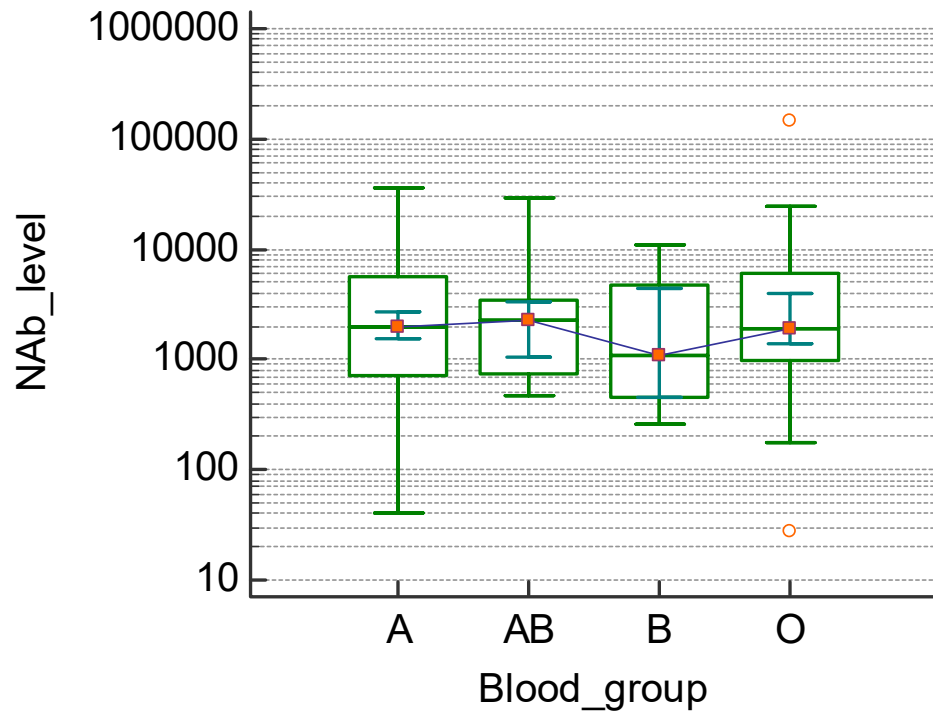


	AFEREZA		PUNA KRV	UKUPNO
period	28.07.20- 28.03.21.		03.05.21.- 30.06.21.	
broj doza	256		464	720
nesukladne	64		140	204
(nizak titar, ostalo) broj (%)	-25%		-30,20%	-28,30%
medijan dobi	36 (18-62)		40 (18-67)	
spol	60,60%	30,40%	100%	
	muškarci	žene	muškarci	
visok titar	75%		91,20%	

- NAb level did not statistically differ between genders.

- ($P = 0.262, Z = 1.12$)



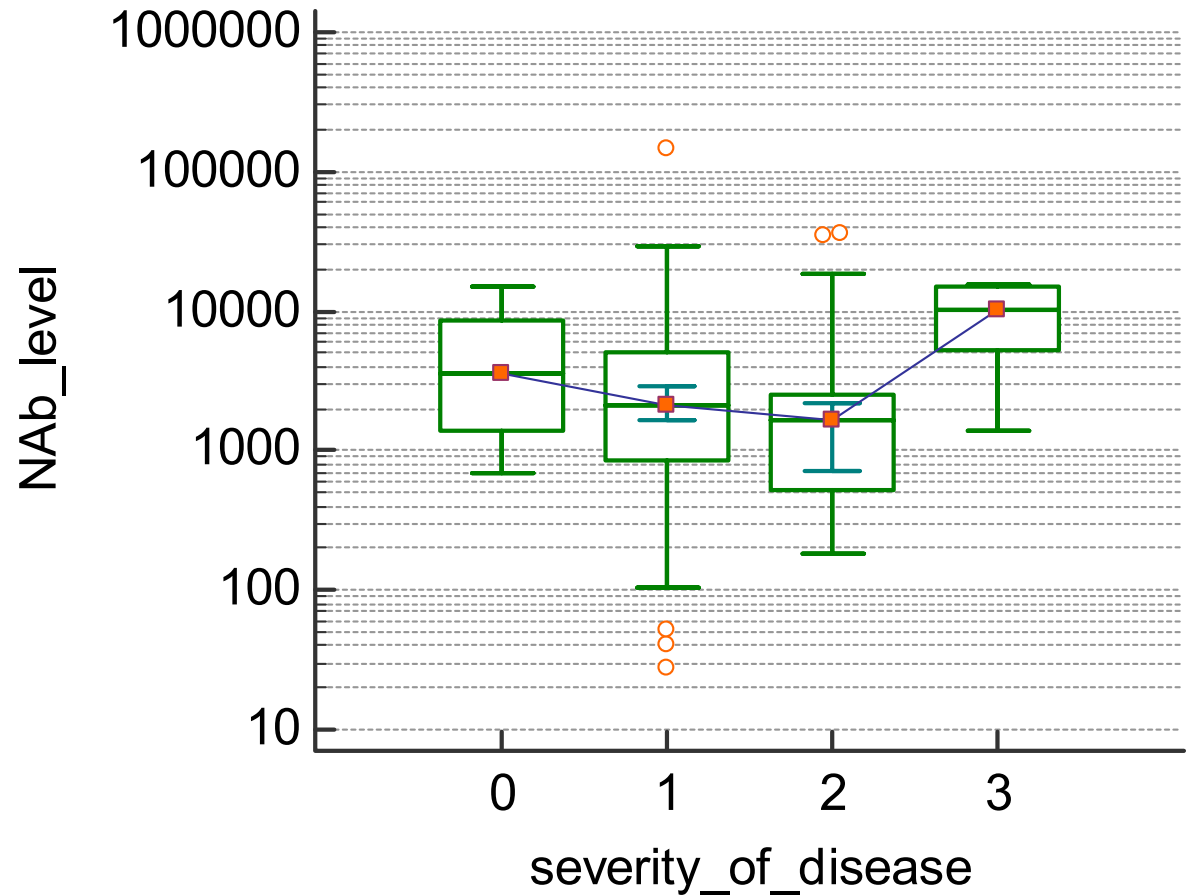


- NAb level did not statistically differ between blood groups.

- ($P = 0.842, \chi^2 = 0.83$)

- NAb level did not statistically differ between severity of symptoms.

- ($P = 0.072, \chi^2 = 6.99$)



a temelju procjene ovih podataka, potencijalna klinička korist od transfuzije COVID-19 rekonvalescentna plazma u hospitaliziranih pacijenata s COVID-19 povezana je s jedinicama visokog titra primjenjuje se u ranoj fazi bolesti. 6 Transfuzija rekonvalescentne plazme COVID-19 u hospitalizirani pacijenti kasno tijekom bolesti (npr. nakon respiratornog zatajenja koje zahtijeva intubacija i mehanička ventilacija) nije povezan s kliničkom dobrom. Ove razmatranja mogu biti različita u bolesnika s potisnutim ili nedostatnim humoralnim imunitetom. Stoga ovaj EUA odobrava samo upotrebu plazme visokog titra rekonvalescentne plazme COVID-19, za liječenje hospitaliziranih pacijenata s COVID-19, u ranoj fazi bolesti. Korištenje niske titar rekonvalescentne plazme COVID-19 nije odobren prema ovom EUA.

FDA odobrenje 23.08.2020. za primjenu cp