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ZNAČAJ BRZE DIJAGNOSTIKE SARS-CoV-2, DOBRE ZDRAVSTVENE ORGANIZACIJE I RAZUMNOG KORIŠĆENJA ZNANJA I RESURSA TOKOM BORBE PROTIV KOVID-19

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SAŽETAK

U decembru 2019. godine pojavila se nova bolest, upala pluća nepoznatog uzroka, povezana sa pijacom morskih plodova u mestu Vuhan (Kina). Na humanim epitelnim ćelijama respiratornog trakta je izolovan jedan nov koronavirus, nazvan prema kliničkoj slici „teški akutni respiratorni sindrom korona virus 2" (SARS-CoV-2), dok je bolest nazvana koronavirusna bolest 2019 (Kovid-19). Pokazalo se da je ova pandemija veliki izazov, kako za stručnjake koji se bave mikorbiološkom dijagnostikom, tako i za sve zdravstvene radnike. Cilj ovog rada je da prikaže značaj brze dijagnostike SARS-CoV-2, značaj zaštite zdravlja zdravstvenih radnika i razumnog korišćenja znanja i resursa tokom borbe protiv Kovid-19. Dosadašnja istraživanja potvrđuju da su u borbi protiv SARS-CoV-2 infekcije od posebnog značaja brza dijagnostika SARS-CoV-2, zaštita zdravlja zdravstvenih radnika i razumno korišćenje znanja i resursa tokom pandemije. Poseban akcenat se stavlja na sprovođenje vakcinisanja protiv sezonskog gripa, kao i protiv invazivne pneumokokne bolesti, jer primenom ovih vakcina možemo olakšati postavljanje dijagnoze Kovid-19 u budućem period u kome se sa velikim nadama očekuje efikasna antivirusna terapija za SARS-CoV-2 i vakcina za Kovid-19.

Ključne reči: Kovid-19, SARS-CoV-2, mikrobiološka dijagnostika, zdravstveni radnici, znanje, resursi

Uvod

Grupa pacijenata sa pneumonijom nepoznatog uzroka povezana je sa pijacom morskih plodova u Vuhanu, u Kini, u decembru 2019. godine. Iz epitelnih ćelija respiratornog trakta čoveka izolovan je novi koronavirus, koji je nazvan prema kliničkoj slici „teški akutni respiratorni sindrom korona virus 2" (SARS-CoV-2). U februaru 2020. godine virus je dobio zvanično ime teški akutni respiratorni sindrom korona virus 2 (engl. *Severe Acute Respiratory Syndrome Corona Virus 2* – SARS-CoV-2). Bolest je dobila ime koronavirusna bolest 2019 (Kovid-19) (1). Procenjeno je da SARS-CoV-2 ima reproduktivni broj (R_0) 2 – 2,5 u prvoj fazi nekontroliranog širenja bolesti, što znači da će se 2 do 3 osobe zaraziti od nultog pacijenta. Grip ima R_0 broj 1,2 (1,2). U prvoj nedelji aprila prijavljen je 1 milion potvrđenih slučajeva i 50.000 smrtnih ishoda (3,4). SARS-CoV-2 virus je izolovan i kod asimptomatskih slučajeva, sa druge strane, neki inficirani pacijenti nastavljaju da budu pozitivni na testu reverzne transkripcije lančane reakcije polimeraze (engl. *Reverse Transcription Polymerase Chain Reaction* – RT-PCR) dve do tri nedelje nakon pojave simptoma (1-3).

Pokazalo se da je Kovid-19 naročito smrtonosna bolest kod starijih pacijenata. U prvoj velikoj studiji iz Vuhana, 137 pacijenata je otpušteno iz bolnice, a 54 je umrlo u bolnici. Većina umrlih pacijenata činili su stariji pacijenti sa komorbiditetima. Pre-življavanje pacijenata kojima je bila potrebna oksigenoterapija takođe je bilo nisko. Preživelo je 20% pacijenata koji su bili na oksigenoterapiji koja je uključivala nazalnu kanilu sa visokim protokom kiseonika u odnosu na 8% preživelih na neinvazivnoj mehaničkoj ventilaciji i 3% preživelih na invazivnoj mehaničkoj ventilaciji (5). SARS-

ACTUAL TOPIC

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THE SIGNIFICANCE OF FAST DIAGNOSTICS OF SARS-COV-2, GOOD HEALTH CARE ORGANIZATION AND REASONABLE USE OF KNOWLEDGE AND RESOURCES IN THE FIGHT AGAINST COVID-19

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SUMMARY

In December 2019, a new disease appeared, that is, pneumonia of unknown cause, which was linked to a seafood market in Wuhan (China). Human respiratory epithelial cells were used to isolate a novel coronavirus, named according to the clinical picture "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2), whereas the disease was named the coronavirus disease 2019 (Covid-19). This pandemic has proved to be a great challenge for all professionals dealing with microbiological diagnostics, as well as for all health care workers. The aim of this work is to present the significance of fast diagnostics of SARS-CoV-2, the significance of protection of health of health care workers, and the reasonable use of knowledge and resources in the fight against Covid-19. The previous research has confirmed that in the fight against the SARS-Cov-2 infection, fast diagnostics of SARS-CoV-2, protection of health of health care workers and reasonable use of knowledge and resources during the pandemic are of utmost importance. A special emphasis is put on the vaccination against seasonal influenza, as well as against the invasive pneumococcal disease because, with the help of these vaccines, the diagnosis of Covid-19 could be made easier in the future period, in which the efficient antiviral therapy for SARS-CoV-2 and the vaccine for Covid-19 are expected with great hopes.

Key words: Covid-19, SARS-CoV-2, microbiological diagnostics, health care workers, knowledge, resources

Introduction to the pandemic of Covid–19

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China. Human airway epithelial cells were used to isolate a novel coronavirus, named according to the clinical picture "severe acute respiratory syndrome 2" (SARS-CoV-2). The virus got an official name in February 2020, Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). The disease was named coronavirus disease 2019 (COVID-19) (1). SARS-COV-2 has an estimated reproduction number (R0) of 2– 2.5 in the first phase of the uncontrolled spreading of the disease indicating that 2 – 3persons will be infected from an index patient. Influenza has R0 of 1.2 (1,2). In the first week of April 1 million confirmed cases, with more than 50,000 deaths were reported (3,4). The SARS-CoV-2 virus has been isolated from asymptomatic individuals, and affected patients continue to be positive on the reverse transcriptase polymerase chain reaction (RT-PCR) test two to three weeks after the start of symptoms (1-3).

COVID-19 has proved to be particularly deadly in elderly patients. In the first major study from Wuhan, 137 patients were discharged from the hospital, while 54 died in the hospital. The vast majority of those who died were the elderly with comorbidities. The survival of patients that needed oxygen support was also bad. 20% of patients on high-flow nasal cannula oxygen therapy survived in comparison to 8% of patients on non-invasive mechanical ventilation and 3% of patients on invasive mechanical ventilation (5). SARS-CoV-2 hit particularly hard

CoV-2 je posebno teško pogodio evropske mediteranske zemlje i njihove starije stanovnike (4). Najteže pogođena regija je bila Lombardija, a većina pacijenata koji su preminuli imali su pridružene bolesti (6).

Pacijenti kod kojih je imunitet kompromitovan predstavljaju grupu pacijenata koji su najviše ugroženi kada je u pitanju Kovid-19. Primećeno je da oboleli od kancera imaju veći rizik od težih formi Kovid-19 bolesti (češće se primaju na odeljenje intenzivne nege i zahtevaju invazivnu ventilaciju, ili kod njih dolazi do smrtnog ishoda) u poređenju sa pacijentima koji nemaju kompromitovan imuni sistem (7-9). „Tri musketara" u borbi protiv SARS-CoV-2 infekcije su brza dijagnostika SARS-CoV-2, zaštita zdravlja zdravstvenih radnika i razumno korišćenje znanja i resursa tokom pandemije (10,11).

Cilj ovog rada je da prikaže značaj brze dijagnostike Kovid-19 bolesti, čuvanja zdravstvenog stanja zdravstvenih radnika i razumnog korišćenja znanja i resursa tokom borbe protiv Kovid-19

Dijagnostika Kovid-19

Trenutno se dijagnostika Kovid-19 bazira na primeni RT-PCR testa. Prvi set opreme je razvijen ubrzo nakon otkrića virusa. U partnerstvu Nemačke i Hong Konga objavljen je članak o razvoju RT-PCR testa (februar, 2020) koji je detektovao i amplifikovao dva različita gena: E (proteinski omotač) i RdRp (RNA-zavisna RNA polimeraza) (5).

Drugi RT-PCR test su dizajnirali Centri za kontrolu i preenciju bolesti Sjedinjenih Američkih Država (engl. *Centers for Disease Control and Prevention* - CDC), koji je mogao da detektuje tri različita gena: područje NS3 je univerzalno za detekciju korona virusa sličnih SARS-u, a N1 i N2 područja su specifična samo za SARS-CoV-2. Testovi su validirani po pitanju svih karakteristika tačnosti (uključujući senzitivnost i specifičnost). Sa trajanjem pandemije brojne kompanije razvijaju i komercijalizuju RT-PCR testove za SARS-CoV-2.

Vreme uzimanja uzorka za analizu se pokazalo kao veoma značajno. Generalno, količina respiratornih virusa je najviša dva dana nakon početka simptoma, te se stoga preporučuje uzimanje uzorka što je pre moguće od početka simptoma. Odlaganje uzimanja uzoraka može da rezultira lažnim negativnim rezultatima, što je generalno karakteristika i ostalih respiratornih virusa. Sposobnost RT-PCR testa da detektuje korona virus u velikoj meri zavisi od kvaliteta uzorka. Ako se nazofaringealni bris (NFB) ne ubaci dovoljno duboko i pravilno u nazofaringealni prostor, odnosno ako se ubaci samo u nozdrve, vrlo je verovatno da će rezultat biti lažno negativan kod pacijenta inficiranog SARS-CoV-2. Prvilno uzimanje uzorka je neophodno, jer ako uzorak nije uzet iz dela gde se virus nalazi, virus neće biti otkriven, bez obzira koliko je RT-PCR test kvalitetan (10). Kod pacijenata sa pneumonijom, savetuje se uzimanje uzorka iz donjeg respiratornog trakta, ali je problem invazivnost metode. Bilo je slučajeva kada je NFB bio negativan, ali je bronhoalveolarna lavaža (BAL) dala uzorak koji je bio pozitivan na RT-PCR testu za SARS-CoV-2 (12).

Postoje problemi i u vezi izvođenja RT-PCR testa. Potrebno je da ga radi veoma iskusno osoblje i zahteva dosta vremena. Takođe, zbog visoke senzitivnosti može da detektuje i kopije gena mrtvog virusa SARS-CoV-2. Evropski centar za prevenciju i kontrolu bolesti (engl. *European Centre for Disease Prevention and Control* - ECDC) savetovao je dodatnu proveru za visoke granične vrednosti (na primer Ct vrednost, engl. *Cycle threshold value*, > 35) RT-PCR testa. Ovaj Centar predlaže da se pozitivni rezultati testa koji imaju visoke Ct vrednosti ponovo razmotre u sklopu osnove kliničke slike (13).

Do sada se zna da je osoba veoma zarazna sve do trenutka kada virus nije moguće izolovati iz ćelijskih kultura. Širenje respiratornog virusa je bilo vrlo visoko tokom prve nedelje simptoma u jednoj nemačkoj studiji (14). Iako je velika količina virusnih RNA dobijana i nakon prestanka simptoma, serokonverzija se javljala nakon 7 dana kod 50% pacijenata. Nijedan virus nije izolovan u ćelijskim kulturama nakon sedmog dana (14,15). I dalje treba uzeti u obzir da jedan negativan test na SARS-CoV-2 (posebno ako je uzorak uzet iz gornjeg respiratornog trakta) ili pozitivan rezultat testa na neki drugi respiratorni patogen, ne isključuju infekciju SARS-CoV-2 (13,16). Ako je prvi RT-PCR test negativan, to ne znači da nije potrebno drugo uzimanje uzorka. Ako pacijent dobije tempe-

the European Mediterranean countries and their elderly inhabitants (4). The area hardest hit by the virus was the region of Lombardy, while the majority of patients in Lombardy who died had the underlying health conditions (6).

Immunocompromised patients are the group of people that are most endangered due to their suppressed immune status when it comes to Covid-19. Patients with cancer were observed to have a higher risk of severe forms of the Covid-19 disease (they are admitted to the intensive care unit more frequently, requiring invasive ventilation, or it comes to deathly outcomes) compared with the patients without the suppressed immune system (7,9). "The three musketeers" of the fight against the SARS CoV-2 infection are the following: fast diagnostics of SARS CoV-2, protection of health of health care workers, and reasonable use of knowledge and resources in the SARS CoV-2 pandemic (10,11).

The aim of this work is to present the significance of fast diagnostics of the Covid-19 disease, protection of health of health care workers, and reasonable use of knowledge and resources during the struggle against Covid-19.

Diagnostics of Covid-19

Current diagnostics is based on RT-PCR test (Reverse transcription polymerase chain reaction). The first kit was developed very soon after the discovery of the virus. The Germany-Hong Kong partnership published the article about the development of the RT-PCR test (February 2020), which detected and amplified two different genes: the E (envelope protein) and RdRp (RNA-dependent RNA polymerase) genes (5).

The United States Centres for Disease Control and Prevention (CDC) designed the other RT-PCR test, which could detect three different genes: the NS3 region for the universal detection of SARS-like coronaviruses, and the N1 and N2 regions, which are specific for SARS-CoV-2. Assays have been validated for all characteristics of precision (including sensitivity and specificity). With the continuation of this pandemic, numerous companies have developed and commercialized RT-PCR tests for SARS-CoV-2.

The time of the collection of samples has proved to be very important. Generally, respiratory viral loads peak two days after the onset of the symptoms, and therefore, the samples are recommended to be taken as soon as possible. Delays in the collection of samples can result in false-negative results, and this is generally true for other respiratory viruses, as well. The ability of the RT-PCR test to detect coronavirus will largely depend on the quality of the sample. If a nasopharyngeal (NP) swab is not inserted deeply and properly into the nasopharyngeal space, that is, if it is inserted only into the nostrils, it is likely that this will result in a false negative result in the patient infected with SARS-CoV-2. The proper collection of samples is needed because if the sample hasn't been collected from an area, where the virus is likely to be, the virus will not be detected regardless of how good the RT-PCR test is (10). In patients with pneumonia, it is advisable to collect the specimen from the lower respiratory tract, but this method can be problematic because it is invasive. We have seen cases when NPS was negative, but the bronchoalveolar lavage (BAL) yielded the sample that was positive for SARS-CoV-2 on the RT-PCR test (12).

There are some problems regarding the RT-PCR test. You need very experienced personnel to do it and is time-consuming. Also, due to its sensitivity, it can detect the copies of genes of dead SARS-CoV-2. The European Centre for Disease Control (ECDC) advised the additional control of high RT-PCR cycle threshold values (e.g. Ct > 35). This Centre suggested that positive test results that have high Ct values should be reconsidered according to the clinical picture (13).

By now we know that person is very contagious till the moment when we are not able to isolate the virus in cell cultures. The respiratory virus shedding was very high during the first week of symptoms in a German study (14). Although shedding a large amount of viral RNA outlasted the end of symptoms, seroconversion occurred after 7 days in 50% of patients. No viruses were isolated in cell cultures after day 7 (14,15). We still have to take into consideration that a single negative SARS-CoV-2 test (especially if from an upper respiratory tract specimen) or a positive test result for another respiratory pathogen does not exclude the SARS-CoV-2 infection (13,16). If the first RT-PCR is negative that does not mean

raturu ili ima respiratorne tegobe, savetuje se ponovno uzimanje drugog uzorka iz donjeg dela respiratornog trakta. Ako je test negativan, treba tražiti druge razloge pogoršanja (11,13). Značan napredak u dijagnozi Kovid-19 infekcije je postignut automatizacijom laboratorijskog procesa. Ovakve sisteme su razvili *Cobas*® *Liat*® (*Roche Molecular 145 Systems, USA*) i *GeneXpert*® (*Cepheid, USA*). Njihova prednost je što se klinički uzorak u medijumu za transport virusa prebacuje u kertridž aparata i što se izvode u laboratorijama biološke bezbednosti klase II/III. Ovi sistemi integrišu izdvajanje virusne nukleinske kiseline (NK), amplifikaciju NK i detekciju specifičnih delova genoma SARS-CoV-2. Osoblje koje radi ove analize treba da ima propisanu zaštitnu opremu (13,16)

SARS-CoV-2 je veoma nepredvidljiv, pa neki pacijenti imaju nespecifične simptome zbog toga je diferencijalna dijagnostika značajna, a trebalo bi da uključi druge respiratorne viruse, *Pneumocystis jirovecii* i atipične bakterije kao što je *Legionella pneumophila*. Zato je ključno da se rezultat RT-PCR na SARS-CoV-2 brzo dobije (slika 1), idealno još tokom pregleda pacijenta (16,18). Postoje dva testa koja daju rezultate za manje od 30 minuta: *ID Now* (*Abbot, USA*) i *Accula SARS-CoV-2 test* (*Mesa Biotech, USA*) (18). Ovi testovi su brzi zato što je korak denaturacije deo procesa i sve se sprovodi na jednoj temperaturi. Oba testa koriste izotermalnu amplifikaciju, i stoga nisu senzitivni kao RT-PCR, a problem može da nastane ako je uzorak krvav ili ako na njemu ima mnogo sluzi. Postoje i brzi antigenski testovi. Jedan od njih je SARS *Sofia* test (*Quidel, USA*). Ovaj test se bazira na flourescentnoj detekciji veze protein – antigena za monoklonska antitela. Za analizu testa je potreban analizator. Za 15 minuta mogu se analizirati dva uzorka. Uzorak je suvi bris NZF. Test je nešto manje senzitivan nego RT-PCR, a treba ga raditi samo kod pacijenata sa simptomima. Sve brze testove je potrebno klinički evaluirati (13).

Perspektive dijagnoze Kovid-19 u sezoni gripa

Budućnost brze i tačne dijagnoze Kovid-19 u sezoni gripa će biti istovremeni „*multiplex*" PCR skrining na veći broj respiratornih patogena, posebno kod dece i imunokompromitovanih pacijenata. Takođe, u nastupajućoj sezoni gripa brza dijagnostika gripa i SARS-CoV-2, na mestu pružanja nege pacijentu, biće ključni korak za smanjenje nepotrebnog korišćenja antibiotika (16,17). Jedno od budućih rešenja jeste i kreiranje višestrukog PCR testa koji može da detektuje sva četiri korona virusa (18,19).

Zdravstveni radnici: njihova uloga i zaštita tokom pandemije Kovid-19

U vreme pandemije SARS-CoV-2, najvažnije je da zdravstveni radnici ne šire virus u populaciji osetljivih ljudi, a posebno na imunokompromitovane pacijente (7,9). Zdravstveni radnici mogu da dobiju virus od pacijenata sa i bez simptoma ako nisu adekvatno zaštićeni. Takođe, SARS-CoV-2 se može preneti sa plastičnih površina i nerđajućeg čelika. Živ virus je otkriven 72 sata nakon kontaminacije ovih površina (20).

Kovid-19 infekcija kod zdravstvenih radnika može biti asimptomatska ili simptomatska (od lake do kritične). Veliki problem predstavlja kada lekari ne znaju svoj status, kako po pitanju Kovida-19, tako i drugih zaraznih bolesti. Ako se zdravstveni radnik inficira ili je bio u visoko rizičnom kontaktu, trebalo bi postaviti standarde kada on može da se vrati na posao. Ako je osoba bila u kontaktu visokog rizika treba da bude u kućnoj izolaciji 14 dana. Ako zdravstveni radnik poseduje specijalna znanja i treba da radi sa svom potrebnom ličnom zaštitnom opremom, onda treba pratiti da li će se kod njega pojaviti simptomi Kovid-19. U slučaju pojave simptoma, treba ga izolovati ili hospitalizovati.

Ako se osoba zarazi, nekoliko zemalja je uvelo standard kada ta osoba može da se vrati na posao. Postoji saglasnost da simptomi treba da nestanu i da, ako ne možemo čekati 14 dana, barem jedan RT-PCR test treba da bude negativan. Italija je takođe postavila standard da je potrebna pojava imunoglobulina G (IgG) da bi se potvrdio status izlečenja (13). IgG serokonverzija je racionalna s obzirom da ako se pojave IgG antitela manje je verovatno da je osoba zarazna (21-23). Serološko testiranje bi moglo biti važno za zdravstvene radnike. Negativni serološki testovi kod zdravih pojedinaca imaju dobru negativnu prediktivnu vrednost. Pozitivan IgG znači da se zdravstveni radnik susreo sa infekcijom SARS-CoV-2 i da je

the second sampling is not necessary. If the patient has a fever or a respiratory discomfort that second sampling is advised from the lower respiratory tract. If the test is negative, we should look for other reasons for deterioration (11-13). The significant advance in diagnostics of Covid-19 was achieved by the automation of the laboratory process. Such systems were developed by are *Cobas® Liat®* (*Roche Molecular 145 Systems, USA*) and *GeneXpert®* (*Cepheid, USA*). Their advantage is that the clinical specimen in the viral transport medium is transferred into a cartridge, in class II/III biosafety laboratories. These systems integrate the separation of viral nucleic acid (NA), the amplification of NA, and the detection of specific genome parts of SARS-CoV-2. Personnel that does these analyses should wear the necessary personal protective equipment (13-16).

SARS CoV-2 is a great pretender, and some patients have non-specific symptoms. Therefore, differential diagnosis is important and it should include other respiratory viruses, *Pneumocystis jirovecii* and atypical bacteria including *Legionella pneumophila* (15) Therefore, the key thing is to get the result of the RT-PCR test for SARS-CoV-2 fast (Figure 1), ideally while examining the patient (16-18). There are two tests that promise the results in less than 30 minutes: *ID Now* (*Abbot, USA*) and *Accula* SARS-CoV-2 test (*Mesa Biotech, USA*) (18). These tests are fast because the denaturation step is part of the process and everything is run on one temperature. Both tests use the isothermal amplification, and therefore, they are not as sensitive as RT-PCR, while problems can arise if the sample is bloody or there is a lot of mucus on it. There are rapid antigen tests, as well. One of them is the *SARS Sofia* test (*Quidel, USA*). This test is based on the fluorescent detection of bond protein-antigen for monoclonal antibodies. The analyzer is necessary for the test analysis. Two samples can be analyzed for 15 minutes. The sample is the NFS. The test is less sensitive than RT-PCR, and it should be done only in patients with symptoms. All rapid tests should be clinically validated.

The perspective of Covid-19 diagnostics in the flu season

The future of the fast and precise diagnostics of Covid-19 during the flu season will be the simultaneous "multiplex" PCR screening for respiratory pathogens, especially in children and immunocompromised patients. Also, during the next flu season, the rapid influenza diagnosis with the rapid point-of-care SARS-CoV-2 diagnosis will be a crucial step that will reduce the unnecessary use of antibiotics (16,17). One of the possible solutions will be the development of the multiplex PCR test, which could detect all four coronaviruses (18,19).

Health care workers: their role and protection during the Covid-19 pandemic

In times of pandemic of SARS CoV-2, the biggest concern of the public is that health care providers do not spread the virus in the population of vulnerable people, especially immunosuppressed patients (7-9). Health care workers can get the virus from patients with or without symptoms if they are not protected properly. Also, SARS-CoV-2 can be transmitted from plastic surfaces and stainless steel. Viable virus was detected up to 72 hours after the contamination of these surfaces (20).

Covid-19 infection in health care workers can be asymptomatic or symptomatic (from mild to critical). Not knowing their status is troublesome in terms of Covid-19 and other infectious diseases. If a health care worker gets infected or had a high-risk contact, we should set standards when he can return to work. If a person had a high-risk contact, he should be in isolation at home for 14 days. If a health care worker has special knowledge, he or she should work protected with all the necessary personal protective equipment and should carefully watch for the symptoms of Covid-19. If symptoms appear, he should be isolated or hospitalized.

If a person is infected, several countries introduced standards when he or she can return to work. It is agreed that the symptoms have to disappear and that at least one PCR has to be negative if we cannot wait 14 days. Italy has also set a standard that the appearance of immunoglobulin G (IgG) is necessary for the confirmation of healed status (13). The standard

zaštićen od dobijanja bolesti bar neki vremenski period. Takvi zdravstveni radnici bi mogli da rade sa pacijentima znajući da se neće razboleti ako ponovo budu izloženi infekciji SARS-CoV-2 i da neće širiti virus. Na slici 2 dat je predlog kako treba da se zaštite zdravstveni radnici tokom pandemije (13).

Razumno korišćenje resursa i znanja tokom pandemije SARS-CoV-2

Etički principi bi takođe trebalo da budu prioritet tokom nege pacijenata u pandemiji SARS-CoV-2. Najvažniji princip je spašavanje života. Međutim, spašavanje života može biti još važnije u uslovima pandemije kada resurse treba mudro koristiti. Razvijanje dodatnih vodiča treba da bude transparentno i inkluzivno i u skladu sa najnovijim saznanjima. Štaviše, diskusija i planiranje su ključni zato što dublja razmatranja nisu izvodljiva tokom javnozdravstvene krize (22). Ako se računa na spašavanje što više života, etično je lečiti nekoga u jedinici Kovid-19 intenzivne nege ko ne želi da prihvati hemoterapiju. Međutim, tu

DIJAGNOZA: PNEUMONIJA?

Oboleli pacijenti sa temperaturom ili drugim siptomima respiratornog trakta (npr. kašalj, kratak dah, hipoksija) su prioritet za testiranje na SARS-CoV-2.

Identifikujte grip, bakterijsku pneumoniju, ili prateće pojave povezane sa lečenjem kao što su post-hirurški plućni problemi ili oni povezani sa sistemskom terapijom (npr. atelektaza, embolija, pneumonitis, edem pluća/višak tečnosti, itd.)

PRIJEM U BOLNICU

Uzmite nazofaringealni bris da biste osobu testirali na SARS-CoV-2 i druge potencijalne respiratorne patogene. Ne zaboravite da uradite krvnu sliku i testove na bakterije npr. *Legionella* i *Streptococcus pneumoniae* antigen iz urina.

Dvostruka infekcija je retka! Moguća je bakterijska superinfekcija.

TEST IZBORA

PRVI IZBOR: Brzi direktni SARS-CoV-2 PCR bez izolacije RNA ili „*multiplex*" PCR za pacijente koji će biti primljeni u jedinicu intezivne nege (respiratorni virusi + SARS-CoV-2 + atipične bakterije).

Prvi izbor za pacijente koji će biti primljeni u bolnicu (samo pacijenti sa simptomima): Ag test na SARS-CoV-2 i influenca tip A i B.

IgG testovi za antitela su adekvatni samo za pacijente koji su imali bolest sličnu Kovid-19 barem 14 dana ranije i voleli bi da provere SARS-CoV-2 status.

Ako je pacijent i dalje sumnjiv na Kovid-19 ili je dobio simptome nalik Kovid-19 tokom hospitalizacije, uradite RT-PCR koji detektuje više od 2 gena iz nazofaringealnog brisa i iz sputuma ili bronhoalveolarnog lavata (BAL-a).

PREDNOSTI I MANE

PREDNOSTI: Brzi direktni PCR/Ag test je adekvatan za pacijente sa jasnim simptomima Kovid-19, a rezultati se dobijaju za manje od 1h, ili „*multiplex*" PCR za 15 minuta. Ovi testovi ne zahtevaju mnogo osoblja i skupu opremu.

MANE: RT-PCR zahteva vreme, direktni RT-PCR/Ag test nije adekvatan za pacijente koji su ozbiljno imunokompromitovani s obzirom da mala količina SARS-CoV-2 može stvarati velike probleme – SARS-CoV-2 pneumoniju.

Slika 1. Dijagnostički algoritam za respiratorne infekcije tokom Kovid-19 pandemije (Evropski centar za prevenciju i kontrolu bolesti) (27)

of IgG seroconversion is rational since if the IgG appears the person is less likely contagious (21-23). Serology testing could be important for health care workers. Negative serology tests in healthy persons have a good negative predictive value. Positive IgG means that a health care worker met with the SARS-CoV-2 infection and that he is protected from getting infected at least for some time. Such health care workers could work with patients knowing that if they were exposed to SARS-CoV-2 again, they would not get ill and would not spread the virus around. The proposed algorithm on how to protect the health care workers during the pandemic is presented in Figure 2 (13).

Reasonable use of resources and knowledge in the SARS-CoV-2 pandemic

Ethical principles should also be our priority while taking care of patients during the pandemic of SARS-CoV-2. The most important principle is saving lives. However, saving lives can be even more important in the conditions of the pandemic when resources should be wisely

DIAGNOSIS: PNEUMONIA?

Patients with fever or other respiratory tract symptoms (eg, cough, shortness of breath, hypoxia) are a priority for testing for SARS-CoV-2.

Identify influenza, bacterial pneumonia, or treatment-related events such as post-surgical lung problems or those associated with systemic therapy (eg atelectasis, embolism, pneumonitis, pulmonary edema/excess fluid, etc.)

HOSPITAL ADMISSION

Take a nasopharyngeal swab to test the person for SARS-CoV-2 and other potential respiratory pathogens. Don't forget to do a blood test and tests for bacteria e.g. *Legionella* and *Streptococcus pneumoniae* antigen from urine.

Double infection is rare! Bacterial superinfection is possible.

TEST OF CHOICE

FIRST CHOICE: Rapid direct SARS-CoV-2 PCR without RNA isolation or multiplex PCR for patients to be admitted to the intensive care unit (respiratory viruses + SARS-CoV-2 + atypical bacteria).

The first choice for patients to be admitted to the hospital (patients with symptoms only): Ag test for SARS-CoV-2 and influenza types A and B.

IgG antibody tests are only adequate for patients who have had a disease similar to Covid-19 at least 14 days earlier and would like to check their SARS-CoV-2 status.

If the patient is still suspected of Covid-19 or has developed Covid-19-like symptoms during hospitalization, perform RT-PCR that detects more than 2 genes from nasopharyngeal swabs and from sputum or bronchoalveolar lavage (BAL)

ADVANTAGES AND DISADVANTAGES

ADVANTAGES: Rapid direct PCR/Ag test is adequate for patients with clear symptoms of Covid-19, and results are obtained in less than 1 hour, or multiplex PCR in 15 minutes. These tests do not require a lot of staff and expensive equipment.

DISADVANTAGES: RT-PCR requires time, direct RT-PCR / Ag test is not adequate for patients who are severely immunocompromised since a small amount of SARS-CoV-2 can create major problems - SARS-CoV-2 pneumonia.

FIgure 1. Diagnostic algorithm for respiratory infections during the Covid-19 pandemic (European Center for Disease Prevention and Control) (27)

Lična zaštitna oprema	Zdravstveni radnik treba da nosi FFP2=N95 maske. One jedino mogu da zaštite da se ne udahne SARS-CoV-2. Dekontaminacija maski nije dokazana u praksi. Ostala zaštitna oprema poput vizira ili naočara i hirurških odela može ponovo da se koristi ako se adekvatno primene mere dekontaminacije.
Visoko rizični kontakt sa osobom koja je pozitivna na Kovid-19	Zdravstveni radnici bi trebalo da ostanu kod kuće 14 dana ili da rade administrativni posao. Ako pokažu znake bolesti slične Kovid-19, treba uzeti uzorak za RT-PCR. Zdravstveni radnici sa specijalnim veštinama mogu da rade sa pacijentima sa FFP2 maskom. Trebalo bi da budu testirani RT-PCR metodom jednom na dva dana ako se zaraze SARS-CoV-2.
Zdravstveni radnik pozitivan na SARS-CoV-2	Treba da bude u izolaciji kod kuće, ili bolje u samoizolaciji, u odvojenom objektu. Kada se radnik oseća dobro i nema temperaturu 2 ili 3 dana može se vratiti na posao. RT-PCR i serologija se radi samo tada, kada se zaposleni vraća na posao ranije nego za 10 dana i ima još simptome Kovid-19. Nalaz IgG za „*spike*" proteina SARS-CoV-2 kod takvog radnika znači da ne može više zaraziti druge osobe.
Zdravlje i održavanje kondicije	Zdravstveni radnik treba da održava kondiciju. Postarajte se da ima svakodnevni kontakt sa porodicom, da spava mnogo i da može da se osloni na podršku kolega. Ne predlažite samoizolaciju radnicima koji su zdravi.
Održavanje pozitivnog duha	Budite kreativni. Zdrava hrana je obavezna. Uključite radnike u proces pripremanja hrane. Ponudite im časove fitnesa unutar ili blizu objekta.
Vakcinacija	Vakcinišite sve koje možete protiv influence tip A i B. Prezentujte im koristi ako se vakcinišu. Ukoliko vakcina za SARS-CoV-2 bude dostupna, organizujte vakcinaciju za sve.

Slika 2. Briga o zdravlju zdravstvenih radnika tokom pandemije Kovid-19 (13)

su i brojna pitanja na koje je teško dati odgovor. Ako ustanova nema dovoljno respiratora za sve Kovid-19 pacijente, da li respirator dati mlađem ili starijem pacijentu sa brojnim komorbiditetima i velikom verovatnoćom za letalni ishod (10,24-26).

Budućnost SARS-CoV-2

SARS-CoV-2 će ostati sa nama kao i četiri korona virusa koji koji u našoj populaciju najviše dominiraju tokom jeseni i proleća. Zato je veoma važno sprovoditi vakcinisanje protiv sezonskog gripa, kao i protiv invazivne pneumokokne bolesti. Uz ove dve vakcine možemo olakšati postavljanje dijagnoze Kovid-19 u budućem periodu u kome se sa velikim nadama očekuje efikasna antivirusna terapija za SARS-CoV-2 i vakcina za Kovid-19.

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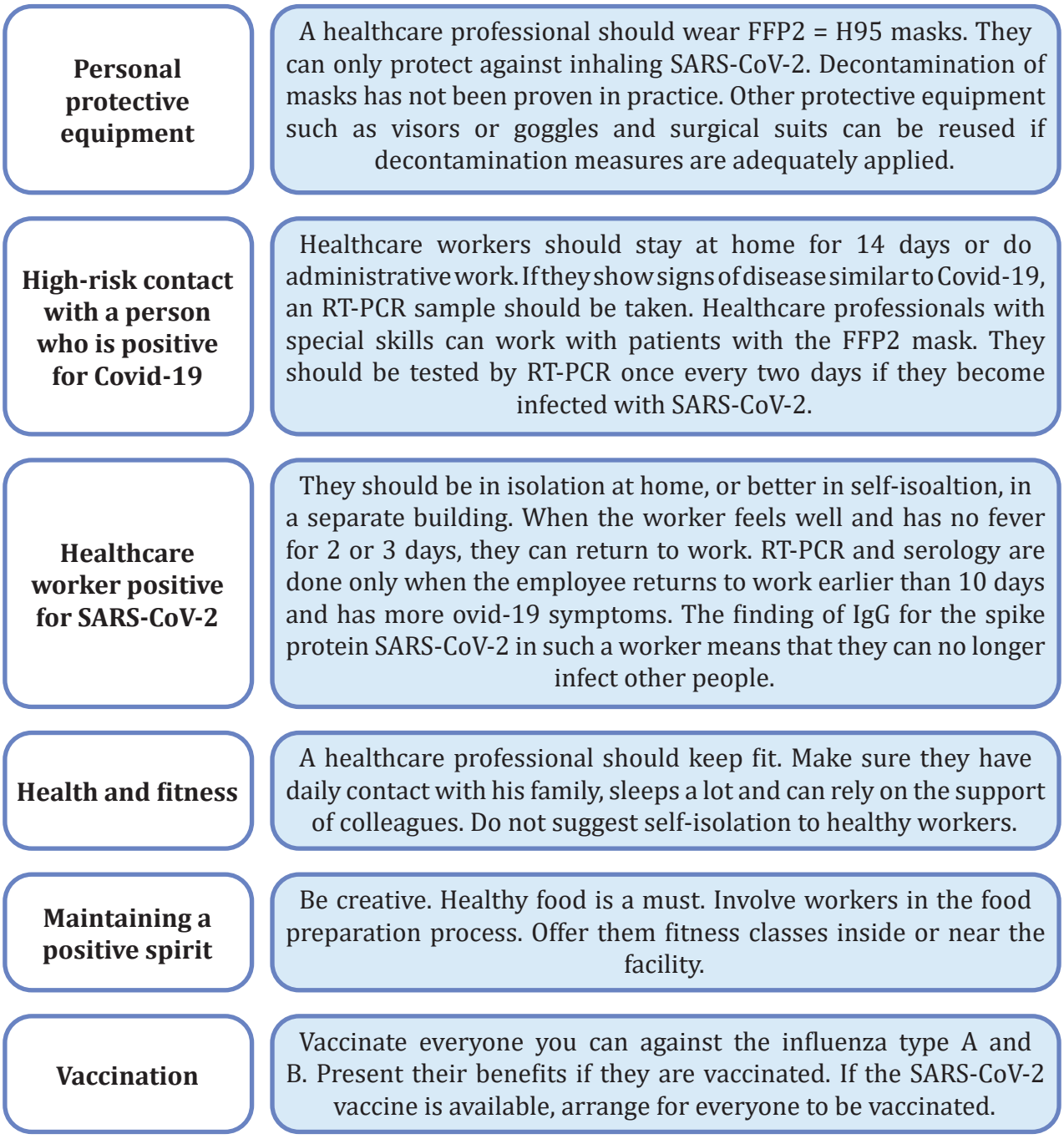

Figure 2. Health care of health workers during the Kovid-19 pandemic (13)

used. Developing additional guides has to be transparent and inclusive, and in accordance with the most recent knowledge. Moreover, discussion and planning are essential because in-depth deliberations are not feasible during a public health crisis (22). If saving the most life counts, is it ethical that we treat somebody in the intensive care Covid-19 unit who does not want to accept chemotherapy. However, there are numerous questions that are difficult to be answered to. If one institution does not have enough ventilators for all Covid-19 patients, should the ventilator be given to a younger patient or the older one with numerous comorbidities and greater possibility for the lethal outcome (10,24-26).

The future of SARS-CoV-2

SARS CoV-2 will stay with us as the other four coronaviruses tthat dominate our population the most during autumn and spring. Therefore, it is very important to conduct vaccination against seasonal influenza, as well as against invasive pneumococcal disease. With these two vaccinations, we can make the diagnosis of Covid-19 easier in the future period, in which

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the efficient antiviral therapy for SARS-CoV-2 and the vaccine for Covid-19 are expected with great hopes.

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