

Review article:

CURRENT CORONAVIRUS (SARS-COV-2) EPIDEMIOLOGICAL, DIAGNOSTIC AND THERAPEUTIC APPROACHES: AN UPDATED REVIEW UNTIL JUNE 2020

Ahmed Nabil^{1, 2, 3, *}, Koichiro Uto¹, Mohamed M. Elshemy⁴, Reham Soliman^{3, 5},
Ayman A. Hassan³, Mitsuhiro Ebara^{1, 6, 7, *}, Gamal Shiha^{3, 8, *}

¹ Research Center for Functional Materials, National Institute for Materials Science (NIMS),
1-1Namiki, Tsukuba, Ibaraki 305-0044, Japan

² Biotechnology and Life Sciences Department, Faculty of Postgraduate Studies for
Advanced Sciences (PSAS), Beni-Suef University, Beni-Suef, Egypt

³ Egyptian Liver Research Institute and Hospital (ELRIAH), Sherbin, El Mansoura, Egypt

⁴ Faculty of Science, Menoufia University, Menoufia, Egypt

⁵ Tropical Medicine Department, Faculty of Medicine, Port Said University, Egypt

⁶ Graduate School of Pure and Applied Sciences, University of Tsukuba, 1-1-1 Tennodai,
Tsukuba, Ibaraki 305-8577, Japan

⁷ Graduate School of Industrial Science and Technology, Tokyo University of Science,
6-3-1 Nijjuku, Katsushika-ku, Tokyo 125-8585, Japan

⁸ Hepatology and Gastroenterology Unit, Internal Medicine Department, Faculty of
Medicine, Mansoura University, Egypt

* **Corresponding authors:** Dr. Ahmed Nabil, Research Center for Functional Materials,
National Institute for Materials Science (NIMS), 1-1Namiki, Tsukuba, Ibaraki 305-0044,
Japan, Tel: (+20)1000618349; 008180-3540-4321,

E-mail: TOLBA.AhmedNabil@nims.go.jp

Mitsuhiro Ebara, Research Center for Functional Materials, National Institute for Materials
Science (NIMS), 1-1Namiki, Tsukuba, Ibaraki 305-0044, Japan. Tel: 008180-6661-5342,

E-mail: EBARA.Mitsuhiro@nims.go.jp

Gamal Shiha, Egyptian Liver Research Institute and Hospital (ELRIAH), Sherbin, El
Mansoura, Egypt; Hepatology and Gastroenterology Unit, Internal Medicine Department,
Faculty of Medicine, Mansoura University, Egypt. Tel: (+20)1223280501,

E-mail: g_shiha@hotmail.com

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ABSTRACT

Coronaviruses are a group of enveloped viruses with non-segmented, single-stranded, and positive-sense RNA genomes. In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in Wuhan City, China. The World Health Organization (WHO) declared the coronavirus outbreak as a global pandemic in March 2020. Fever, dry cough and fatigue are found in the vast majority of all COVID-19 cases. Early diagnosis, treatment and future prevention are keys to COVID-19 management. Currently, the unmet need to develop cost-effective point-of-contact test kits and efficient laboratory techniques for confirmation of COVID-19 infection has powered a new frontier of diagnostic innovation. No proven effective therapies or vaccines for SARS-CoV-2 currently exist. The rapidly increasing

research regarding COVID-19 virology provides a significant number of potential drug targets. Remdesivir may be the most promising therapy up till now. On May 1, 2020, Gilead Sciences, announced that the U.S. Food and Drug Administration (FDA) has granted emergency use authorization (EUA) for the investigational Remdesivir as a potential antiviral for COVID-19 treatment. On May 7, 2020, Gilead Sciences, announced that the Japanese Ministry of Health, Labour and Welfare (MHLW) has granted regulatory approval of Veklury® (Remdesivir) as a treatment for SARS-CoV-2 infection, the virus that causes COVID-19 acute respiratory syndrome, under an exceptional approval pathway. Also, Corticosteroids are recommended for severe cases only to suppress the immune response and reduce symptoms, but not for mild and moderate patients where they are associated with a high-risk side effect. Based on the currently published evidence, we tried to highlight different diagnostic approaches, side effects and therapeutic agents that could help physicians in the frontlines.

Keywords: COVID-19, SARS-CoV-2, Remdesivir, Diagnosis, Epidemiology, Therapy

INTRODUCTION

In December 2019, a novel coronavirus, SARS-CoV-2, was identified as the pathogen causing coronavirus disease (COVID-19) in Wuhan, China. On March 11, 2020, the World Health Organization declared COVID-19 as a global pandemic (Whitworth, 2020).

COVID-19 is an enveloped, positive-sense, single-stranded RNA virus that belongs to the beta-CoV genus, which also includes SARS-CoV and MERS-CoV. It shares 89 % nucleotide identity with bat SARS-like CoVZXC21 and 82 % identity with human SARS-CoV (Chan et al., 2020a).

COVID-19 is transmitted by inhalation or contact with infected droplets. The incubation period for COVID-19 is on average, 5–6 days, but can be up to 14 days. During this period, also known as the “presymptomatic” period, some infected persons can be contagious, from 1–3 days before symptom onset (Wei et al., 2020). The clinical manifestations of COVID-19 varied from asymptomatic carrier status, acute respiratory disease (ARD) and pneumonia. The prevalence of asymptomatic cases is significant (20–86 % of all infections) and is defined as individuals with positive viral nucleic acid tests but without any COVID-19 symptoms. Most people with COVID-19 develop only mild (40 %) or moderate (40 %) disease, approximately 15 % develop a severe disease that requires hospitalization and oxygen support, and 5 % have a critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS),

sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury (CDC, 2020b) Older age, co-morbidities such as diabetes, hypertension, cardiac disease, chronic lung disease, cancer and BMI > 40 kg/m² have been reported as risk factors for severe disease and death (CDC, 2020a).

COMMON SIGNS AND SYMPTOMS

Wang and colleagues (2020a) reported that there are 6 common signs and symptoms that 30 % of the patients have felt including fever (98.5 %), fatigue (69.9 %), dry cough (59.4 %), anorexia (39.8 %), myalgia (34.8 %), dyspnea (31.1 %) and for the most common comorbidities are hypertension (31.1 %) and cardiovascular disease (14.5 %). Symptoms may develop 2 days to 2 weeks following exposure to the virus (CDC, 2020b). According to Wu and McGoogan (2020), among 72,314 SARS-CoV-2 cases reported to the Chinese Center for Disease Control and Prevention (CCDC), 81 % were mild (mild or absent pneumonia), 14 % were severe (dyspnea, hypoxia, > 50 % lung involvement within 1-2 days), 5 % were critical (respiratory failure, shock, multiorgan dysfunction), and 2.3 % were fatal. Symptoms in children with infection appear to be uncommon, although some children with severe COVID-19 have been reported (CDC, 2020a). Based on currently available information and clinical expertise, risk factors for severe COVID-19 include older adults ≥ 65 years as well as people of all

ages with chronic lung disease or moderate to severe asthma, serious heart conditions, diabetes, severe obesity, chronic kidney disease, liver disease and immunocompromised people (CDC, 2020a).

SUGGESTED INFECTION MECHANISM

Upon infection with COVID-19, it binds to the host cell's angiotensin-converting enzyme 2 (ACE2) receptors which commonly expressed on the epithelial cells of alveoli, trachea, bronchi, and bronchial serous glands of the respiratory tract. Then the virus enters and replicates in these cells (Liu et al., 2011). The newly developed virions are then released and infect new target cells. Unfortunately, there is no specific antiviral treatment or vaccine recommended for COVID-19 that is currently available.

CURRENT EPIDEMIOLOGICAL SITUATION

According to the European Centre for Disease Prevention and Control (ECDC), since 31 December 2019 and as of 14 June

2020, 7,759,691 cases of COVID-19 have been reported including, most cases in America (n = 3788548) were reported from the United States (2,074,526), Brazil (850,514) and Peru (225,132), followed by Europe (n = 2,170,600): most cases were reported in Russia (520,129), United Kingdom (294,375) and Spain (243,605), Asia (n = 1557541): most cases were in India (320,922), Iran (184,955) and Turkey (176,677), Africa (n = 233528): most cases were in South Africa (65,736), Egypt (42,980), Nigeria (15,682), Oceania (n = 8766): most cases were in Australia (7,290), New Zealand (1,154) and Guam (185) (Figure 1), including 430,127 deaths, most deaths in America (n = 201,874) were reported from the United States (115,436), Brazil (42,720) and Mexico (16,872), followed by Europe (n = 182674): most deaths were in United Kingdom (41,662), Italy (34,301) and France (29,398), Asia (n = 39147): most deaths were in India (9,195), Iran (8,730) and Turkey (4,792), Africa (n = 6294): most deaths were in Egypt (1,484), South Africa (1,423) and Algeria (760), Oceania (n = 131): most deaths were in Australia (102), New Zealand (22) and Guam (5) (ECDC, 2020).

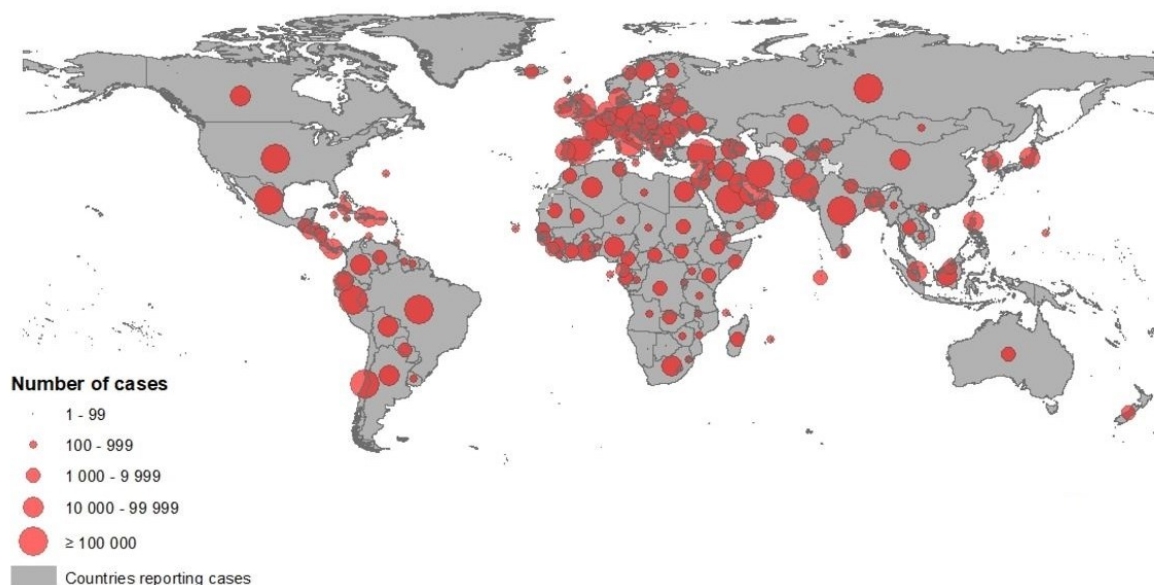


Figure 1: Novel coronavirus COVID-19 geographical distribution over the world 2020-05-09 (ECDC, 2020)

The countries that beat COVID-19 were divided into three groups as follows: countries beating COVID-19: green plots (Figure 2), countries that are nearly there: yellow plots (Figure 3) and countries that need to take action: red plots (Figure 4). These plots adjusted for each country to better show the data. The vertical axis is plotted in arbitrary units, to easily compare the shapes of the curves (EndCoronavirus, 2020).

SARS-COV-2 DIAGNOSIS

The diagnosis of COVID-19 mainly depends on the demonstration of the virus in respiratory secretions by special molecular tests.

Common laboratory findings include normal/low white cell counts with elevated C-reactive protein (CRP). The computerized tomographic chest scan is usually abnormal even in those with no symptoms or mild disease (Singhal, 2020). In addition to laboratory testing capacity and reagent shortages, the rapidly growing SARS CoV 2 pandemic has encouraged many diagnostic manufacturers to develop and sell fast and easy-to-use equipment to facilitate testing outside the laboratory (WHO, 2020a).

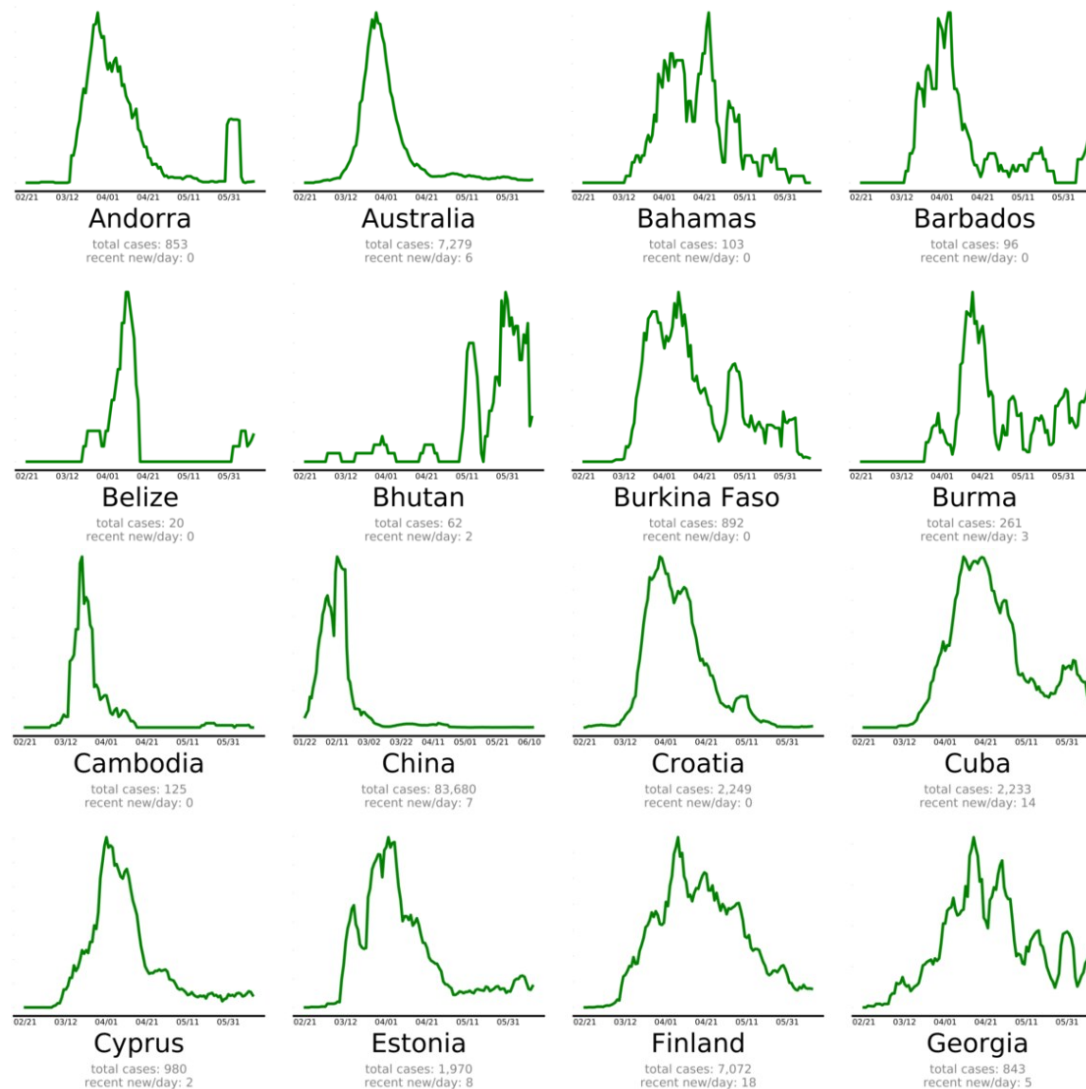


Figure 2: Countries beating COVID-19 in alphabetical order (EndCoronavirus, 2020)

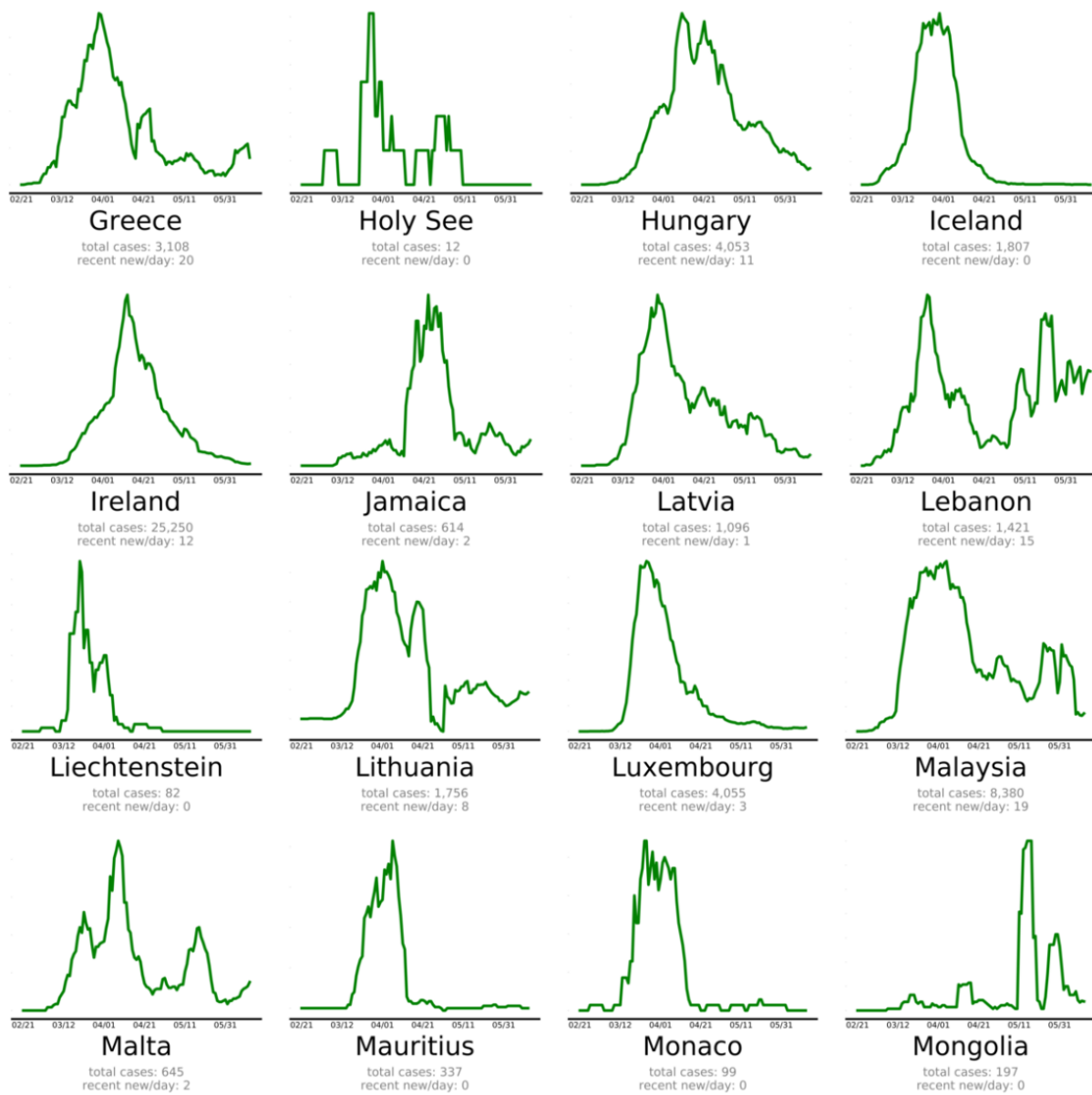


Figure 2 (cont.): Countries beating COVID-19 in alphabetical order (EndCoronavirus, 2020)

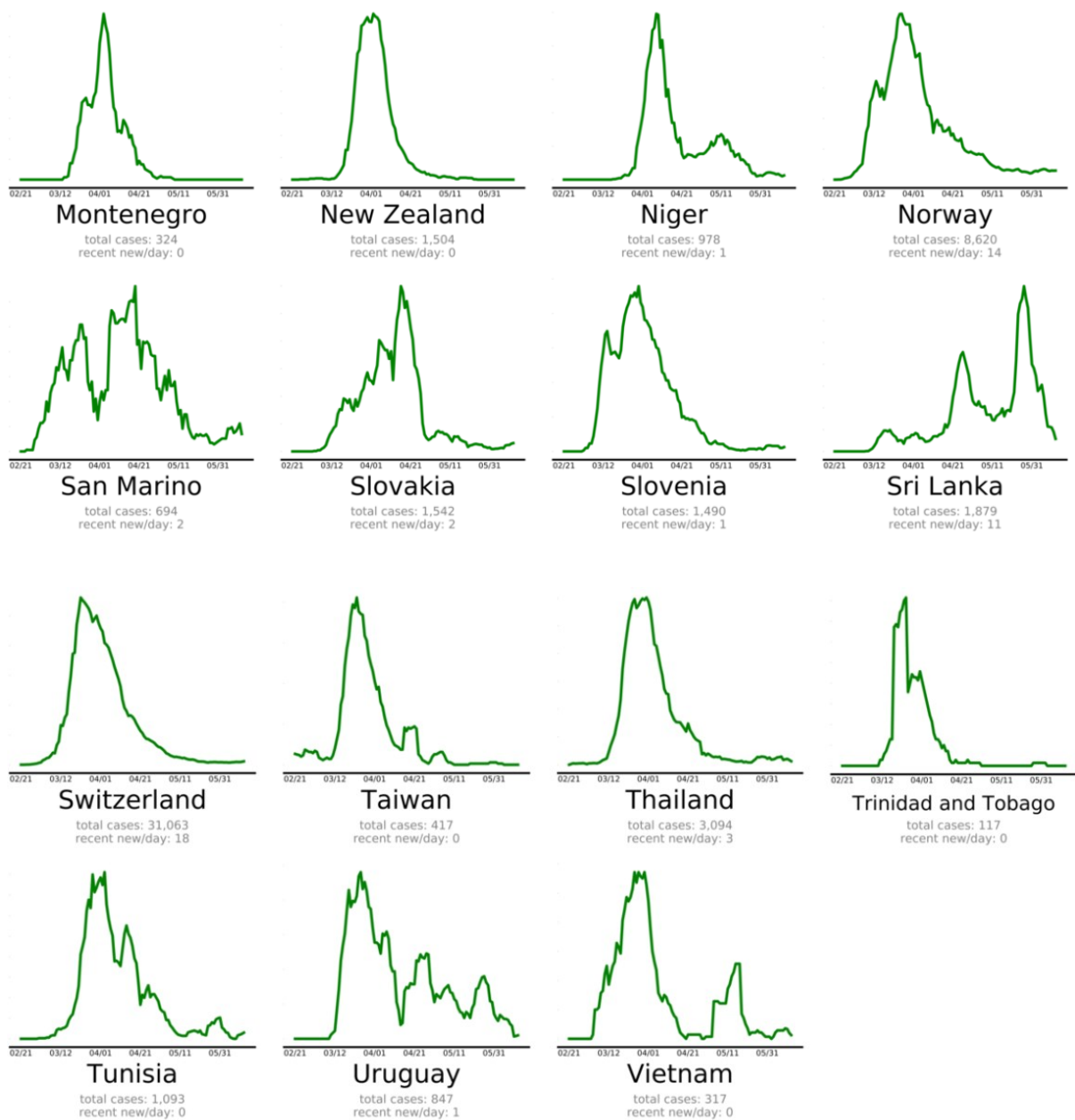


Figure 2 (cont.): Countries beating COVID-19 in alphabetical order (EndCoronavirus, 2020)

Currently, there are two main categories commercially available for COVID-19 tests. The first category includes molecular assays for detection of SARS-CoV-2 viral RNA using polymerase chain reaction (PCR)-based methods. The second category includes serological and immunological assays that largely depend on detecting antibodies produced by individuals as a result of exposure to the virus

or on the detection of antigenic proteins in infected individuals. It is necessary to ensure that these two categories of tests serve overlapping purposes in the management of the SARS-CoV-2 pandemic (Carter et al., 2020). Current COVID-19 diagnostic tools and techniques are shown in Table 1 and a diagnostic model for COVID-19 in Figure 5.

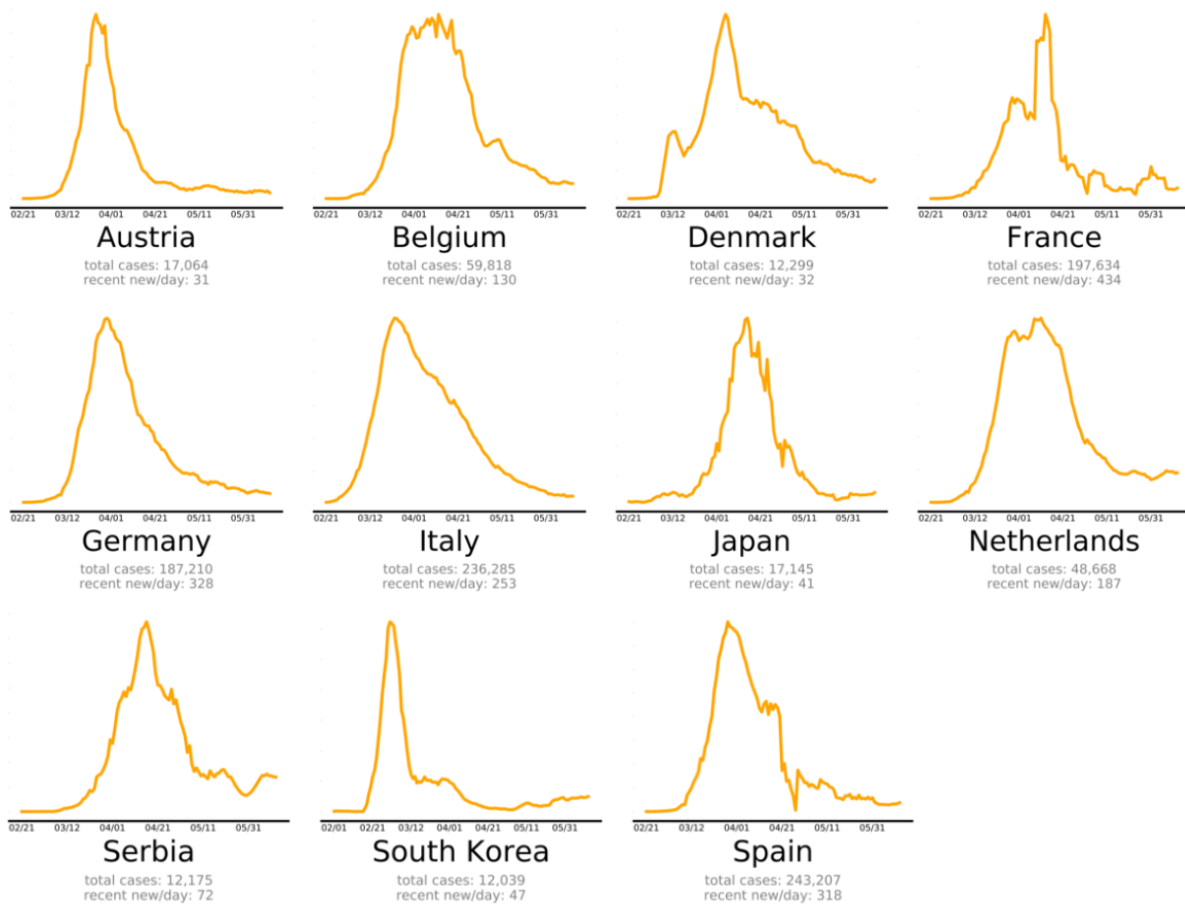


Figure 3: Countries that are nearly there (EndCoronavirus, 2020)

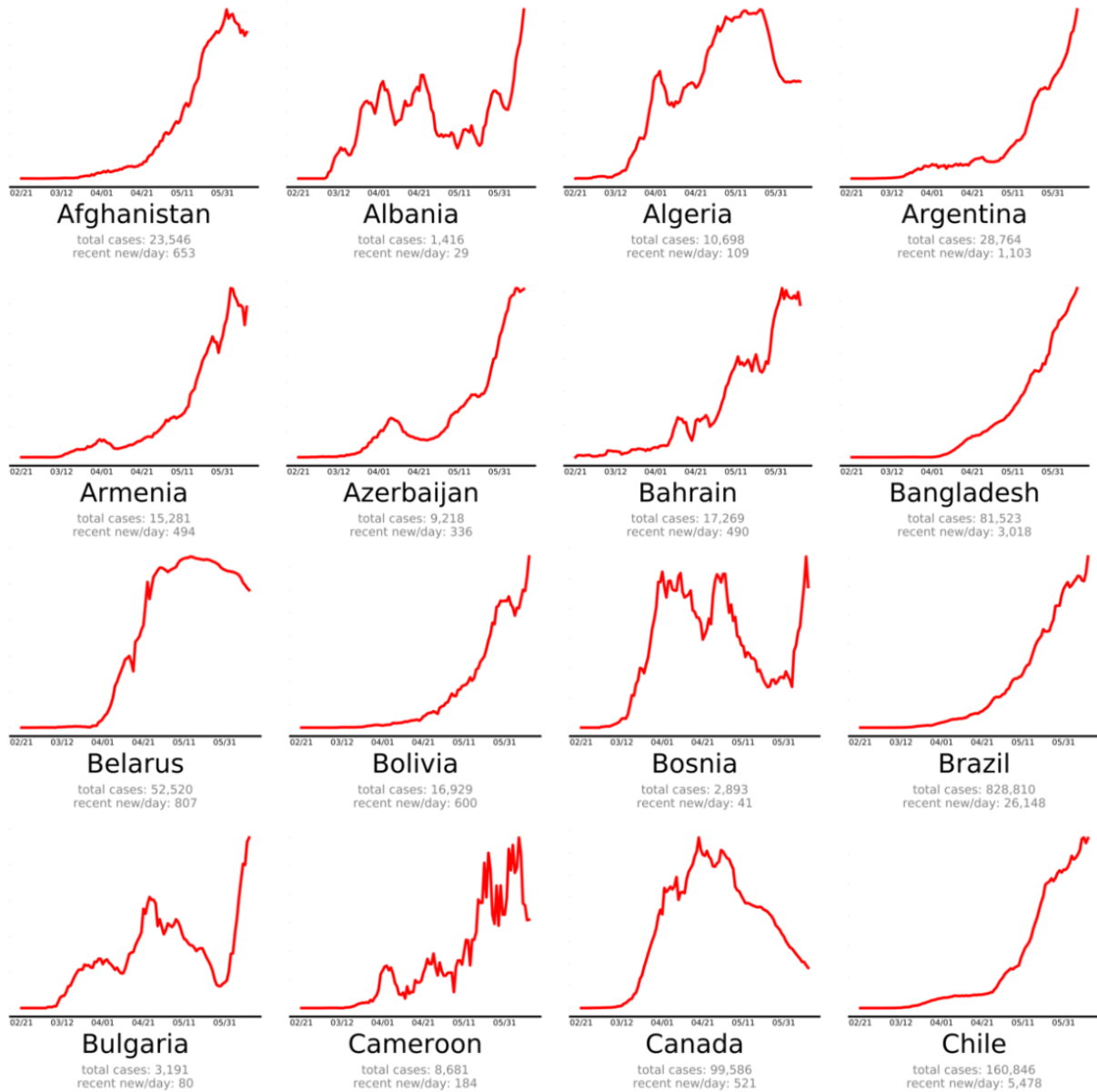


Figure 4: Countries that need to do an action (EndCoronavirus, 2020)

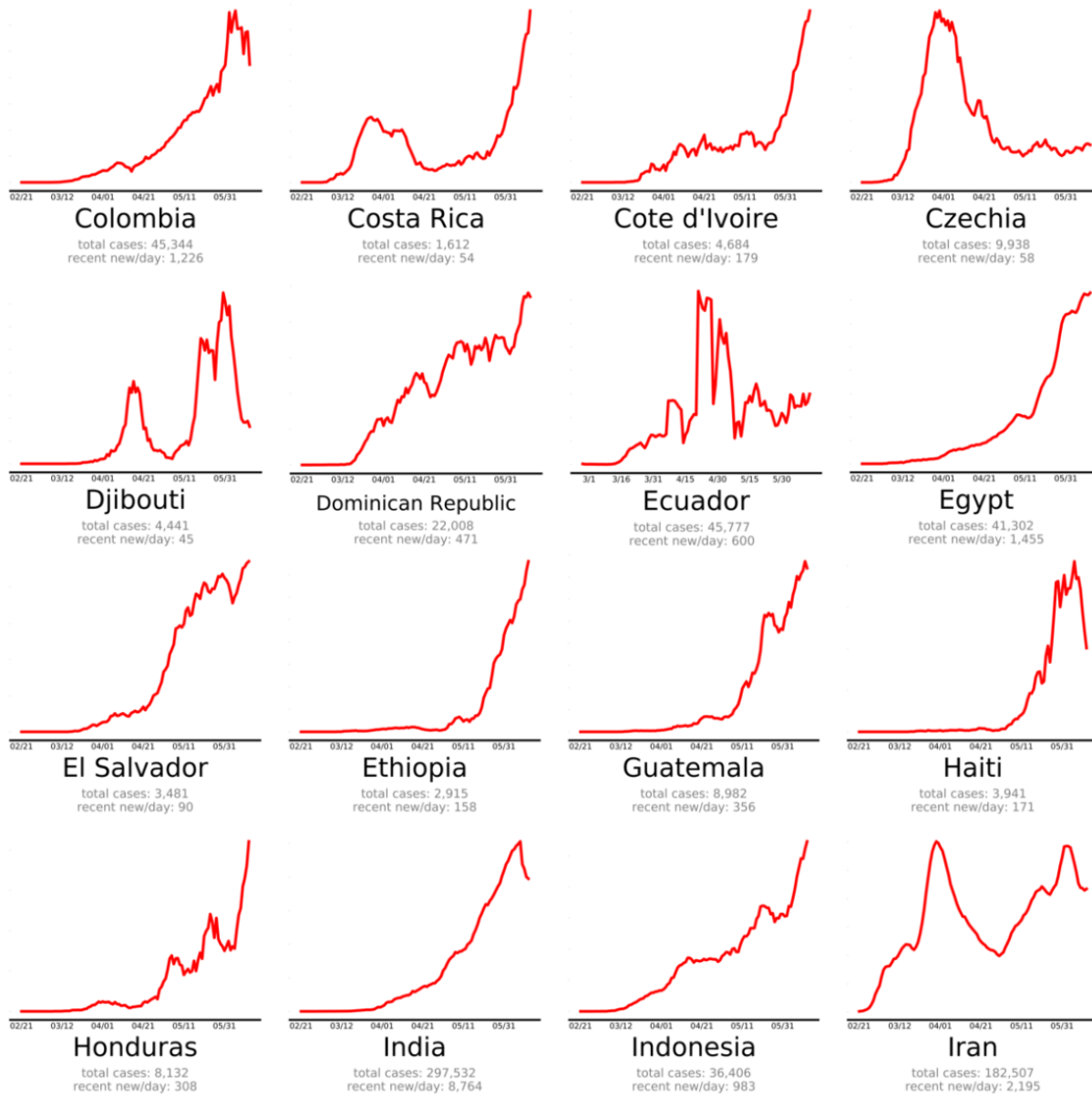


Figure 4 (cont.): Countries that need to do an action (EndCoronavirus, 2020)

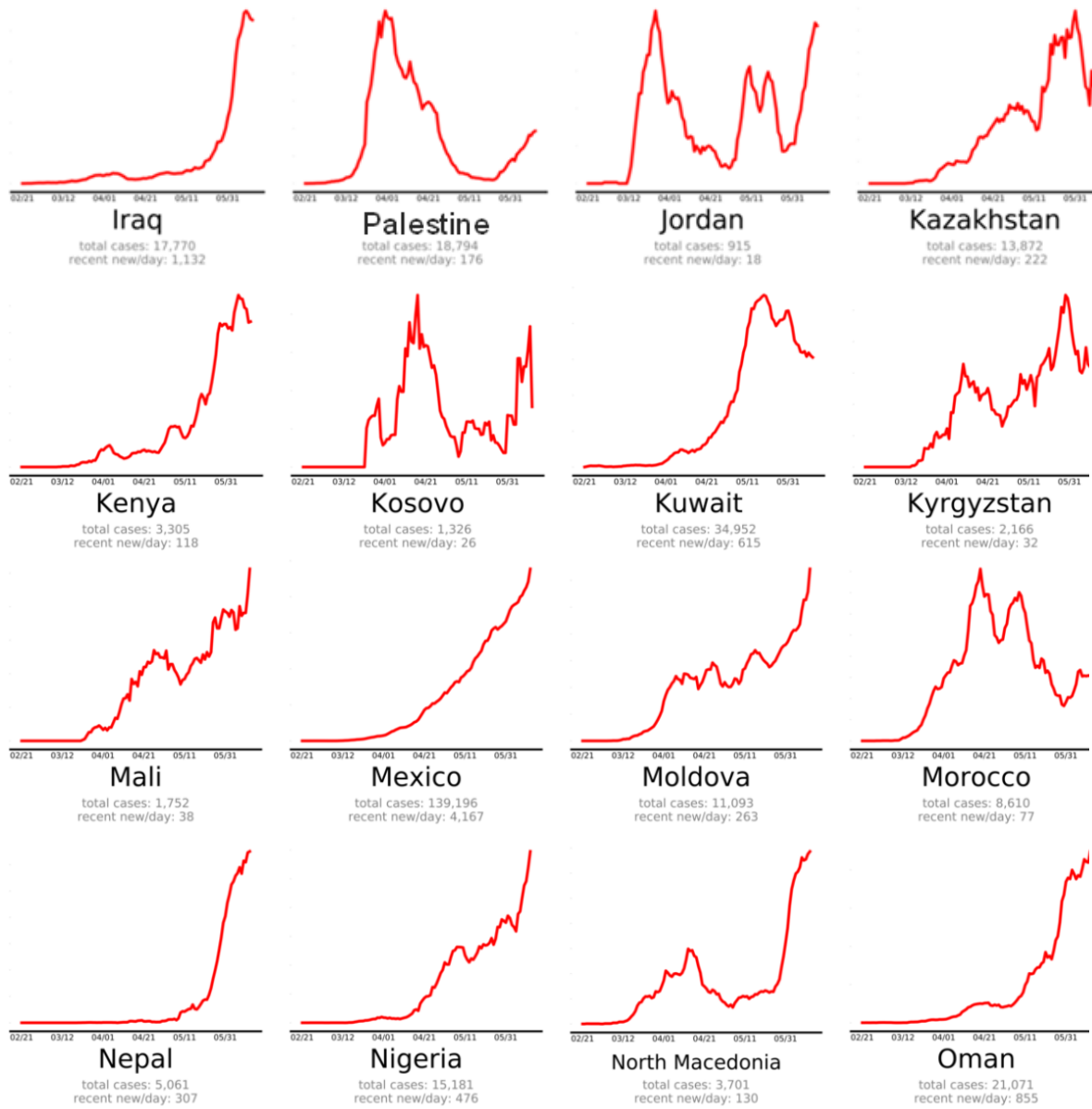


Figure 4 (cont.): Countries that need to do an action (EndCoronavirus, 2020)

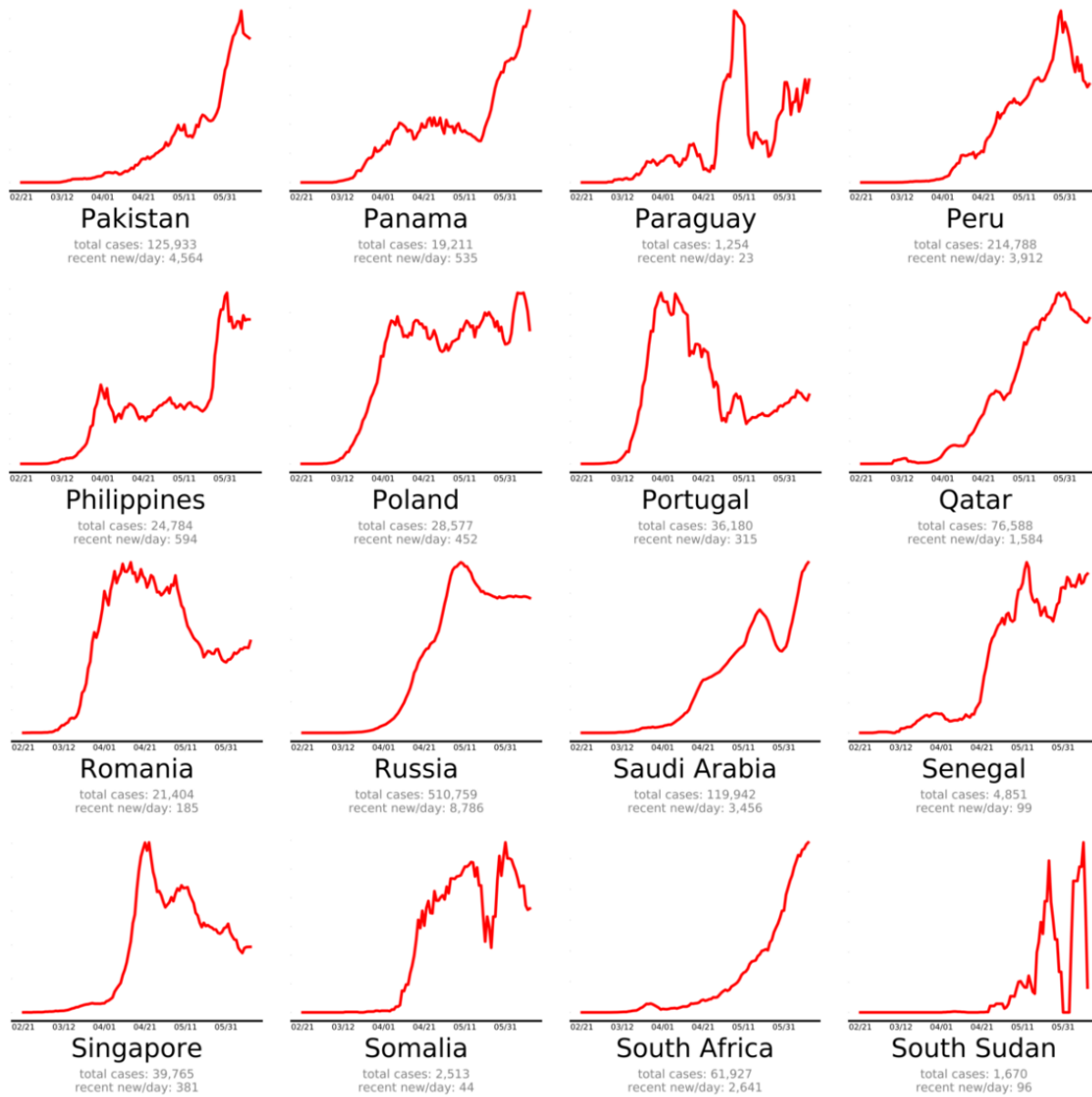


Figure 4 (cont.): Countries that need to do an action (EndCoronavirus, 2020)

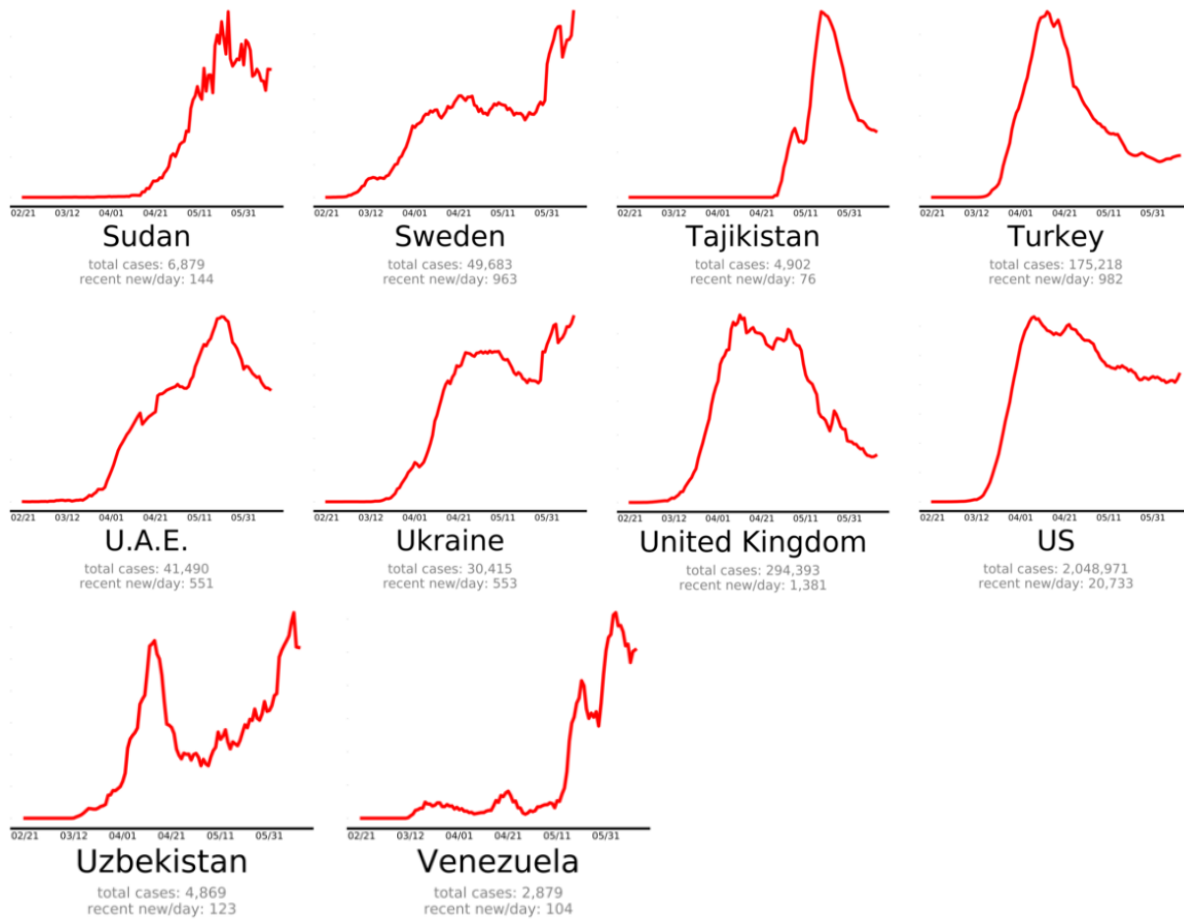


Figure 4 (cont.): Countries that need to do action (EndCoronavirus, 2020)

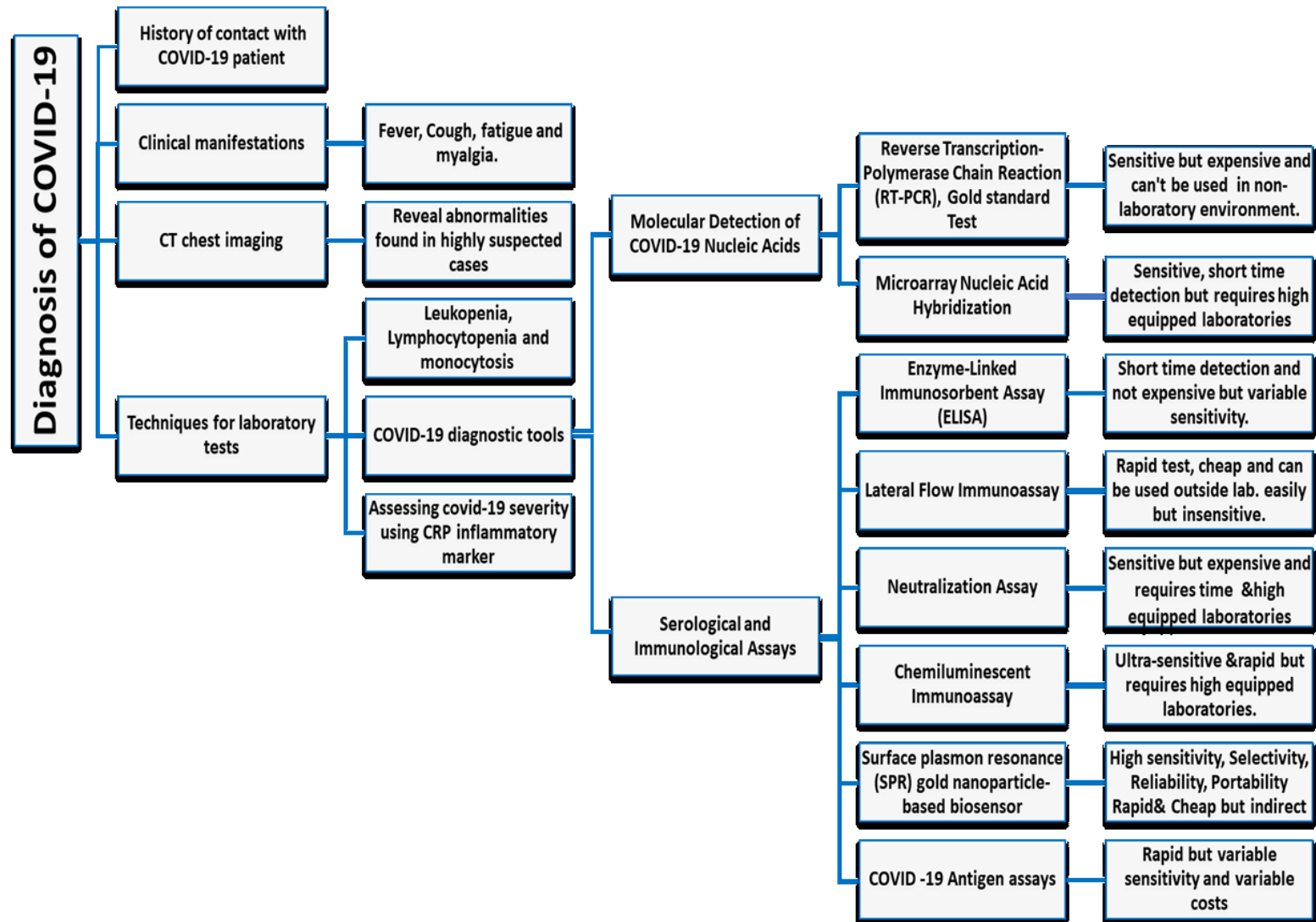


Figure 5: The Diagnostic Model for COVID-19

Table 1: Current SARS-CoV-2 diagnostic tools and techniques

Category	Test	Principle	Sample	Advantages	Disadvantages	Reference
1- Molecular Detection of COVID-19 Nucleic Acids	a- Reverse Transcription-Polymerase Chain Reaction (RT-PCR) (gold standard test)	This assay based on the conversion of a short sequence of COVID-19 genomic RNA to complementary DNA copy (cDNA) using specific RNA-dependent DNA polymerase. This process is known as reverse transcription followed by real-time RT-PCR, amplification and detection of DNA.	Upper respiratory system samples especially nasopharyngeal swab	Sensitive, gold standard test	Time-consuming, expensive, requires high laboratory infrastructure, well-trained staff and cannot be used in a non-laboratory environment	Chan et al., 2020b
	b- Microarray Nucleic Acid Hybridization	The process starts with reverse transcription followed by cDNA loading into specific wells containing Covid-19 specific oligonucleotides fixed on their surfaces. After washing the viral DNA remains hybridized, emitting signals that indicate a positive result.	Upper respiratory system samples especially nasopharyngeal swab	Sensitive, requires a short time	Expensive, requires high laboratory infrastructure, well-trained staff and cannot be used in a non-laboratory environment	Chen et al., 2010
2- Serological and Immunological Assays	a- Enzyme-Linked Immunosorbent Assay (ELISA)	COVID-19 ELISA plate wells are coated with a COVID-19 antigen. This process starts with adding of patient sample to the coated well if the sample contains anti-COVID-19 antibody, so it will bind specifically, forming an antigen-antibody complex that can be detected by another labeled secondary antibody that produces a color or fluorescence.	Blood serum or plasma	Requires a short time, not very expensive	Variable sensitivity, requires high laboratory infrastructure, well-trained staff and cannot be used in a non-laboratory environment	Carter et al., 2020
	b- Lateral Flow Immunoassay	A rapid diagnostic test, patient samples are applied to a nitrocellulose membrane that contains immobilized COVID-19 antigen and allows the flowing of the sample. If the sample contains anti-CoV-19 antibodies, it will be trapped with a specific antigen causing the color band visualization.	Blood serum or plasma	Rapid test about 10 minutes, cheap, can be used in a non-laboratory environment, very simple and easy to be used	Insensitive	Wang et al., 2005

Table 1 (cont.): Current SARS-CoV-2 diagnostic tools and techniques

Category	Test	Principle	Sample	Advantages	Disadvantages	Reference
	c- Neutralization Assay	The patient sample is added to COVID-19 infected cell culture. If the patient sample contains anti-CoV-19 antibodies, it inhibits viral replication in COVID-19 infected cell cultures.	Whole blood, serum, or plasma	Sensitive	Time-consuming, expensive, requires high laboratory infrastructure, well-trained staff and cannot be used in a non-laboratory environment.	Whiteman et al., 2018
	d- Chemiluminescent Immunoassay	An automated serological diagnostic test, patient samples are added to specific reagents, contain antibody specific for anti-COVID-19 labeled by chemiluminescent substance followed by chemiluminescent substance excitation and after returning to its stable state, it will emit photons that can be detected by chemiluminescent signal instrument.	Blood serum or plasma	Ultra-sensitive, rapid	Expensive, requires high laboratory infrastructure, well-trained staff and cannot be used in a non-laboratory environment.	Cai et al., 2020
	e- Surface Plasmon Resonance (SPR) gold nanoparticle-based biosensor	Depending on using a coronaviral surface antigen decorated by gold offering a stable, specific sensitive platform for COVID-19 antibody detection	Blood serum or plasma	High sensitivity, selectivity, rapid, cheap, reliability, portability, can be used in non-laboratory environment, easily to be manufactured	This method is an indirect method, where it detects antibody, so developing of SPR biosensor to detect COVID-19 itself still is a great challenge.	Park et al., 2009
	f- COVID-19 Antigen Assays	Based on the detection of COVID-19 antigen using its specific antibody, depending on ELISA, lateral flow and chemiluminescent assays	Blood serum or plasma	Rapid	Variable sensitivity, variable costs	Carter et al., 2020

SARS-COV-2 DIFFERENT THERAPEUTIC APPROACHES

Symptomatic treatment and oxygen therapies represent the major treatment interventions for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen

therapy, whereas hemodynamic support is essential for managing septic shock (Cascella et al., 2020).

To the best of our knowledge, different therapeutic approaches have been evaluated against COVID-19 *in vivo*, *vitro* and in clinical trials. Many of these therapies had a great impact on clinical recovery. Current COVID-19 therapies are shown in Table 2.

Table 2: Different SARS-CoV-2 therapeutic approaches and mechanisms

	Treatment	Mechanism of action	Reference
1	Chloroquine and Chloroquine phosphate	Well known anti-malarial agents beside their efficacious as anti-inflammatory agents with autoimmune cases including rheumatoid arthritis and <i>Lupus erythematosus</i> . Chloroquine and Chloroquine phosphate have slightly alkaline pH, so both can increase the endosomal pH of the host cells, and suppress virus/cell fusion as well as interfering with the glycosylation of cellular receptors of SARS-CoV and finally causing a significant inhibitory effect on viral infections. So, anti-viral and anti-inflammatory activities of Chloroquine and Chloroquine phosphate may account for their potent efficacy in treating patients with COVID-19 pneumonia.	Gao et al., 2020
2	Lopinavir/ Ritonavir (LPV/r) Combined Therapy	Both Lopinavir and Ritonavir are protease inhibitors, this combination can block viral replication. Lopinavir is considered actually to be the agent that acts on the virus. Ritonavir is a CYP3A inhibitor that reduces Lopinavir metabolism, thereby boosting Lopinavir levels.	Lim et al., 2020; Cao et al., 2020
3	Teicoplanin	Teicoplanin acts on the early step of the viral life cycle by inhibiting the low pH cleavage of the viral spike protein by cathepsin L in the late endosomes thereby preventing the release of genomic viral RNA and the continuation of the virus replication cycle.	Baron et al., 2020
4	Remdesivir	Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in premature termination. May 1, 2020, Gilead Sciences, announced that the U.S. Food and Drug Administration (FDA) has granted emergency use authorization (EUA) for the investigational Remdesivir as a potential antiviral for COVID-19 treatment. May 7, 2020, Gilead Sciences, announced that the Japanese Ministry of Health, Labour and Welfare (MHLW) has granted regulatory approval of Veklury® (Remdesivir) as a treatment for SARS-CoV-2 infection, the virus that causes COVID-19 acute respiratory syndrome, under an exceptional approval pathway.	Wang et al., 2020b; Devaux et al., 2020
5	Arbidol and Arbidol mesylate	Arbidol and Arbidol mesylate were shown to have a direct antiviral effect in early viral replication <i>in vitro</i> for SARS-CoV.	Deng et al., 2020a

Table 2 (cont.): Different SARS-CoV-2 therapeutic approaches and mechanisms

Treatment	Mechanism of action	Reference	
6	Inhibitors of Renin-Angiotensin System (RAS)	Both SARS and SARS-CoV-2 invade the cell through the ACE2 receptor. SARS-CoV reduces ACE2 expression, causing an imbalance between the ACE/Ang II/AT1R axis and the ACE2/Ang (1–7)/Mas receptor axis. A novel therapeutic strategy for hypertension targets the ACE/Ang II/AT1R axis. Angiotensin-Converting Enzyme Inhibitors (ACEIs) and agents acting on the renin-angiotensin system (ARAS) inhibit the ACE/Ang II/AT1R pathway in addition to modulation of the ACE2/Ang (1–7)/Mas receptor pathway. COVID-19 patients observed to have a dysfunction in the renin-angiotensin system (RAS). It was also noticed that ACEI/angiotensin-receptor blockers (ARB) had the potential to decrease the viral load, regulate immune function and inhibit inflammatory responses.	Sun et al., 2020a; Meng et al., 2020
7	Protease Inhibitors	SARS-coronaviruses enter the host cells by activation their envelope glycoproteins using the host cell proteases. SARS-coronaviruses use cell surface serine proteases for their activation. So, cysteine protease inhibitors interfere with viral cell invasion and effectively prevent viral spread.	Zhou et al., 2015
8	Mesenchymal Stem Cells (MSCs)	MSCs transplantation improved the outcome of COVID-19 patients. These findings may be due to regulating inflammatory response and promoting tissue repair and regeneration, where mesenchymal stem cells are blank cells that can differentiate into most cellular types in addition to their paracrine fashion of cytokines and growth factors that dampen inflammation and cell death.	Leng et al., 2020
9	Tocilizumab	Well-known recombinant humanized anti-human interleukin-6 receptor monoclonal antibody that is mainly used for rheumatoid arthritis patients. In COVID-19 infection, a massive number of T-lymphocytes and mononuclear macrophages are activated, emitting different cytokines such as interleukin-6 (IL-6), which binds to the IL-6 receptor on its target cells, causing the cytokine storm and severe inflammatory responses in most organs including lungs, liver, kidney and other tissues and organs. Tocilizumab can specifically bind soluble interleukin-6 receptor (sIL-6R) and membrane-bound interleukin-6 receptor (mIL-6R) and inhibits their signal transduction.	Xu et al., 2020a
10	Human monoclonal antibody	Coronavirus neutralizing antibodies target the viral trimeric spike (S) glycoproteins that exist on the viral surface and mediate viral entry into the host cells.	Li et al., 2020
11	Baricitinib	Most viruses invade cells through receptor-mediated endocytosis. ACE2 is the receptor that COVID-19 uses to infect lung cells. ACE2 is a cell surface protein that distributed many cells including kidney, blood vessels, heart, and, especially, lung AT2 alveolar epithelial cells. AT2 cells are mainly prone to viral infection. One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1). Disruption of AAK1 might, in turn, interrupt the passage of the virus into cells and also the intracellular assembly of virus particles. Baricitinib with therapeutic dosage (2 mg or 4 mg once daily) is sufficient to inhibit AAK1.	Richardson et al., 2020
12	COVID-19 recovered patients' convalescent plasma	COVID-19 recovered patients' convalescent plasma contains a huge quantity of COVID-19 monoclonal antibodies. So, direct administration of COVID-19 recovered patients' convalescent plasma might suppress viremia. Several studies showed a shorter hospital stay and lower mortality rate in convalescent plasma-treated patients than those who were not treated with it.	Chen et al., 2020

Table 2 (cont.): Different SARS-CoV-2 therapeutic approaches and mechanisms

Treatment	Mechanism of action	Reference	
13	Indinavir/Remdesivir combined therapy	Docking studies proved that both Indinavir/Remdesivir have low docking scores and docking sites which overlap with the protein pockets effectively. So, it is expected that this combined therapy can block the replication of COVID-19 RNA. These 2 drugs have limited cytotoxicity, so they are highly recommended for COVID-19 treatment.	Chang et al., 2020
14	Nelfinavir	Nelfinavir was recommended to be used as a potential therapy for COVID-19 through inhibition of its main protease using an integrative approach combining molecular docking, homology modeling and binding free energy calculation.	Xu et al., 2020b
15	Regulation of interferon production	The DNA sensor cyclic GMP–AMP synthase (cGAS), anaplastic lymphoma kinase (ALK) and stimulator of interferon genes (STING) were suggested to be potential therapeutic effective targets preventing the cytokine storm during COVID-19 infection.	Deng et al., 2020b
16	Direct Acting Antivirals (DAAs)	Currently, FDA approved drugs that target specific viral nonstructural proteins and lead to disruption of viral replication and infection include Sofosbuvir, Ribavirin, and Remdesivir. There are 4 classes of DAAs, which are classified by their mechanism of action and their targets. Nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs) and NS5A inhibitors. These drugs were recently used for HCV treatment in Egypt (recovery rate about 99 %). DAAs are suggested to be possible inhibitors for COVID-19 by binding COVID-19 RNA dependent RNA polymerase (RdRp). DAAs can be used against the novel strain of coronavirus with promising results.	Elfiky, 2020
17	Human umbilical cord mesenchymal stem cells (HUCMSCs)	HUCMSCs have shown significant tissue repair and immunomodulation with a low immunogenic effect that makes these cells very ideal candidates for the allogenic adoptive transfer therapy. HUCMSCs were also suggested to be a potential treatment for H5N1 infection-induced acute lung injury. COVID-19 showed a similar inflammatory cytokine profile to that of H5N1.	Liang et al., 2020
18	CD-sACE2 Inclusion Compounds	The main receptors for SARS-CoV and SARS-CoV-2 are ACE2 Soluble ACE2 (sACE2) retaining ACE2 enzyme activity in addition to binding SARS-CoV S-protein. So sACE2 can inhibit SARS-CoV infected cells. Since SARS-CoV and SARS-CoV-2 infection mechanisms are the same, sACE2 can inhibit the infection of SARS-CoV-2. To improve the water solubility of sACE2, the formation of a complex between CD and sACE2 would be effective and enables it to meet drug atomization inhalation requirements.	Sun et al., 2020b
19	Favipiravir (Avigan®)	Favipiravir is a Pyrazine carboxamide broad-spectrum antiviral drug that has been approved in Japan for influenza treatment. It is a pro-drug that is phosphorylated and ribosylated intracellularly to form its active metabolite (Favipiravir ibofuranosyl -5'-triphosphate) that acts as a competitive inhibitor for viral purine nucleosides in addition to inhibition of RNA-dependent RNA polymerase (RdRp) of RNA viruses. Finally, it interferes with viral replication.	Du and Chen, 2020
20	Ivermectin	FDA-approved for parasitic infections treatment. Caly et al. reported that Ivermectin has the potential to inhibit COVID-19 <i>in vitro</i> by interfering with the nuclear import of host and viral proteins, where its single treatment was able to cause ~5000-fold reduction in COVID-19 virus after 48 h in cell culture model.	Caly et al., 2020

Table 2 (cont.): Different SARS-CoV-2 therapeutic approaches and mechanisms

Treatment	Mechanism of action	Reference	
21	β -d-N4-hydroxycytidine (NHC; EIDD-1931)	Orally bioavailable prodrug (β -d-N ⁴ -hydroxycytidine-5'-isopropyl ester) has been reported to improve pulmonary function and reduces COVID-19 titer through induction of transition mutation frequency in viral RNA causing lethal mutagenesis of COVID-19.	Sheahan et al., 2020
22	Atazanavir	Atazanavir inhibits the activity of COVID-19 essential protease, causing a decline of viral replication in addition to its ability to stop the cytokine storm-associated mediator releasing. So, it acts both as an anti-inflammatory and antiviral candidate.	Fintelman-Rodrigues et al., 2020
23	Recombinant Human Erythropoietin	It has a protective effect on lung tissue by inhibiting NF- κ B expression in lung tissues, inhibition of IL-6 and TNF-alpha as proinflammatory cytokines and induction of anti-inflammatory cytokine IL-10.	Hadadi et al., 2020
24	Ribavirin	It is a guanosine analog that interferes with RNA and DNA virus's replication through interference with viral polymerases and interference with RNA capping. It was shown to have limited value for the treatment of COVID-19 as monotherapy with high cytotoxicity but when used in combination with other agents it provided the best chance for clinical efficacy.	Graci and Cameron, 2006; Sanders et al., 2020
25	Corticosteroids	Corticosteroids are mainly used for decreasing the host inflammatory responses into the lungs which may lead to acute lung injury and acute respiratory distress syndrome (ARDS) but corticosteroids may have adverse effects, including delayed viral clearance and the high risk of secondary infection. Moreover, direct evidence for corticosteroids in the treatment of COVID-19 is limited.	Russell et al., 2020
26	Lianhua-qingwen (Anti-Viral and Anti-Inflammatory)	Traditional Chinese medicine that has been previously used for influenza treatment with broad-spectrum anti-influenza effects. Lianhua-qingwen was found to inhibit COVID-19 replication <i>in vitro</i> with a significant reduction in pro-inflammatory cytokines (TNF- α , IL-6, CCL-2/MCP-1 and CXCL-10/IP-10).	Runfeng et al., 2020
27	Anticoagulant treatment	Low molecular weight heparin appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer. An interventional clinical trial on 128 participants in Xijing Hospital showed that the early use of aspirin in COVID-19 patients, which has the effects of inhibiting virus replication, anti-platelet aggregation, anti-inflammatory and anti-lung injury, is expected to reduce the incidence of severe and critical patients, shortens the length of hospital duration and reduces the incidence of cardiovascular complications.	Tang et al., 2020; clinicaltrials.gov, 2020

SARS-COV-2 THERAPEUTIC APPROACHES - SIDE EFFECTS

Despite the approved beneficial effects of these therapeutic approaches, recent studies concluded that most of these candidate's administration has a toxic effect in overdoses, causing common and severe adverse effects including nausea, pruritus, arrhythmias, hypoglycemia, anemia, jaundice, hyper-

lipidemia, electrolyte abnormalities, acute renal injury, hematological disorders, hyperuricemia, neuropsychiatric effects and various drug-drug interactions.

Chloroquine (CQ) interferes with ventricular repolarization that increases the risk of torsades de pointes (TdP) and may cause sudden cardiac death (Ursing et al., 2020), also it causes neuropsychiatric manifestations in-

cluding confusion agitation, psychosis, mania, hallucinations, paranoia, suicidal ideation, depression, insomnia and catatonia (Aneja et al., 2019) as well as severe hypoglycemia (El-Solia et al., 2018). Moreover, CQ has severe immunological mediated adverse effects including drug reaction with eosinophilia and systemic symptoms (DRESS) (Girijala et al., 2019), Stevens-Johnson syndrome (Leckie and Rees, 2002) and toxic epidermal necrolysis (Cameron et al., 2014).

Lopinavir/Ritonavir (LPV/r) combination has been reported to have gastrointestinal disorders, so in some SARS-CoV-2 patients, the treatment was stopped due to these severe side events (Owa and Owa, 2020). Notwithstanding the minimal side effects of Teicoplanin, it may cause thrombocytopenia in some treated cases (Terol et al., 1993).

A recent clinical trial regarding Remdesivir with severe COVID-19 patients concluded that adverse events including hypokalemia, constipation, hypoalbuminemia, anemia, jaundice, hyperlipidemia, liver enzyme elevation and thrombocytopenia were reported (Wang et al., 2020c).

An exploratory randomized controlled trial assessing the efficacy and safety of Arbidol in COVID-19 patients reported that patients had adverse events including diarrhea, nausea and loss of appetite (Eikenberry et al., 2020), also hypotension, acute renal injury, teratogenicity, hypersensitivity, electrolyte abnormalities, fatigue, diarrhea, weakness, anemia and chest pain are the most common risk factors during treatment of COVID-19 patients using inhibitors of the renin-angiotensin system (Ingraham et al., 2020).

Zhang and colleagues (2020) reported that intravenous transplantation of Wharton's jelly derived mesenchymal stem cells (hWJCs) was safe and effective especially, in COVID-19 critical severe cases. Regarding Tocilizumab that was used as a treatment for severe COVID-19 cases, it may cause serious adverse reactions, like intestinal perforation, candidiasis and lipid metabolism abnormalities (Tao et al., 2020).

FDA has approved convalescent plasma therapy in COVID-19 critical patients, but up till now, only three studies with small sample size reported effectiveness and safety so more clinical trials are needed to ensure both safety and efficacy (Bloch et al., 2020).

Otherwise Direct-acting antivirals (DAAs) demonstrated, a safe therapeutic approach with common side effects including fatigue, headache, nausea and neuropsychiatric symptoms (Medeiros et al., 2017). Concerning using of Favipiravir (Avigan®) as a treatment for COVID-19 patients, it was reported that Favipiravir elevates plasma uric acid, so this finding should be considered in hyperuricemia, gout and kidney impairment patients (Mishima et al., 2020).

Despite the beneficial effect of Corticosteroids with COVID-19 patients, they are associated with a high risk of death, side effects like bacterial infections and hypokalemia so they are not recommended for mild and moderate COVID-19 patients, but they should be used in severe cases only to suppress the immune response and reduce symptoms (Yang et al., 2020).

CHLOROQUINE TRIGGERS OXIDATION AND HEMOLYTIC ANEMIA IN G6PD DEFICIENT CASES & WORLD HEALTH ORGANIZATION DISCONTINUED ITS TREATMENT TRIALS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common human enzymatic disorders affecting around 400 million people worldwide (Luzatto and Arese, 2018). Decreased G6PD production results in low levels of NADPH and reduced glutathione stimulating hemolytic anemia which is characterized by oxidative stress and red blood cell lysis (Francis et al., 2013).

The risk of hemolytic anemia should be considered during Chloroquine/Hydroxy Chloroquine (CQ/HCQ) therapy of patients with G6PD deficiency (Mohammad et al., 2018).

Beauverd and colleagues (2020) reported that SARS-CoV-2 infection can enhance severe acute hemolysis in patients with G6PD-deficiency, and CQ/HCQ can worsen this crisis. During the treatment of SARS-CoV-2, it is important to carefully monitor potential hemolytic effects of CQ/HCQ in G6PD deficiency cases. If a decline in hemoglobin levels during the first days of CQ/HCQ treatment is observed, the treatment should be stopped. Hemolysis usually is reversible after finishing therapy with CQ/HCQ (De Franceschi et al., 2020). Also, Kapoor and Kapoor (2020) warned of the use of CQ because of the risk of hematological disorders in patients with G6PD deficiency.

In contrast, both (Youngster et al. 2010; Beutler 1994) concluded that CQ or HCQ mono-therapies are safe also in G6PD deficient cases.

Afra and colleagues (2020) reported that infections might be the most common causes of hemolysis in G6PD deficient patients. Thus, SARS-CoV-2 patients may show significant hemolysis even before CQ or HCQ administration.

Finally, SARS-CoV-2 treatment using CQ or HCQ, especially in areas with high G6PD deficiency prevalence, should alert medical staff to this possible harmful effect. The US Food and Drug Administration warned of cardiotoxicity caused by hydroxychloroquine and mentioned G6PD as a baseline test before the onset of hydroxychloroquine treatment (FDA, 2020). Moreover, in July 2020 the WHO discontinued clinical trials with hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19 (WHO, 2020b), where both therapies produced little and no reduction in the mortality of hospitalized SARS-CoV-2 cases when compared to standard of care.

CONCLUSION

Finally, COVID-19 pandemic is a highly infectious disease caused by the novel coronavirus SARS-CoV-2 that can be transmitted through droplets and close contact and repre-

sents a global public health crisis. Fever, fatigue and dry coughs are the most common signs and symptoms of COVID-19. Due to rapid transmission, countries around the world should increase attention to disease surveillance systems. SPR gold nanoparticle-based biosensors may be a promising diagnostic technique as it had high sensitivity, selectivity, reliability, portability, is rapid and cheap, but this method is an indirect method, where it detects antibody, so developing of SPR biosensor to detect COVID-19 itself still is a great challenge. No proven effective therapies or vaccines for SARS-CoV-2 currently exist. The most promising therapy up till now maybe Remdesivir, also we recommend Corticosteroids therapy for severe cases only to suppress the immune response and reduce symptoms, but not for mild and moderate patients where they are associated with high-risk side effects. G6PD should be considered as a baseline test for starting CQ or HCQ treatment protocol to avoid its possible hemolytic effect. We should further strive to develop specific medications, support the research and development of vaccines, and also decrease morbidity and death of SARS-CoV-2 to preserve the population.

Authors contribution

Ahmed Nabil: Resources, Conceptualization, Original draft writing, Supervision, Review & Editing. Koichiro Uto: Original draft writing, Review & Editing. Mohamed M. Elshemy: Original draft writing, Review, Editing & Resources. Reham Soliman: Writing, Review & Editing. Ayman A. Hassan: Writing & Editing. Mitsuhiro Ebara: Conceptualization, Resources, Original draft writing, Supervision, Review & Editing. Gamal Shiha: Conceptualization, Original draft writing, Review, Editing & Supervision.

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Conflict of interest

The authors declare that they have no conflict of interest.

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