

# A Review of Covid-19 Detailed study of History, Life cycle, Diagnosis and Prevention of Corona virus

## ABSTRACT:

Coronavirus Disease-2019 is a new life-threatening, quickly-spreadable pandemic disease. It is a huge family of viruses known to cause sickness from breathing trouble, fever, fatigue, cough, sore throat, breathlessness, and common cold to the continuation of acute respiratory tract infection and the severity of the infection sometimes visible as pneumonia, acute respiratory syndrome and even death. The disease is commonly known as COVID-19. Since December 2019, Covid-19 emerged in Hunan seafood market at Wuhan in South China and rapidly spreading throughout the world, the virus epidemic has been proclaimed a public health emergency of International concern by World Health Organization (WHO). An exceedingly infectious potential for spreading resulted in the universal coronavirus disease 2019 (COVID-19) pandemic in 2020. Though some specialists cast doubts that the virus is transmitted from animals to humans, there are mixed results on the origin of coronavirus. In this review, we go through the history of covid-19, virus life cycle, diagnosis, and prevention with reference to the historical coronavirus pandemic in 2002.

Keywords: COVID-19, SARS, Symptoms, Respiratory syndrome, Treatment.

## 1. INTRODUCTION:

“Up until the SARS outbreak (2002), coronaviruses only displayed their possibility for epidemic spread and significant pathogenicity in humans, and were mainly known as the cause of mild respiratory syndrome and gastrointestinal disease” [1]. “Over the past two decades three novel Beta coronaviruses drastically altered such a perception, these are the Severe Acute Respiratory Syndrome (SARS-CoV), Middle East Respiratory Syndrome (MERS)-CoV and SARS-CoV2, in which the viruses crossed the species barrier and caused significant epidemic characterized by increased case-fatality rates in humans” [2–4]. “The small re-emergence of SARS in late 2003 after the restarting of the wildlife market in southern China and the current discovery of a very similar virus in horseshoe bats, the bat SARS-Coronavirus, suggested that SARS can return if circumstances are fit for the introduction, amplification, mutation, and transmission of this threatening virus” [5-8]. “Seven coronaviruses can bring about infection among people around the world but people mostly get infected with four human coronaviruses, 229E, NL63, OC43, and HKU1” [9]. “The virus typically spreads rapidly from one person to another via respiratory droplets and aerosol produced through coughing and sneezing. It’s considered most infectious when people are symptomatic, although transmission may be achievable before symptoms show up in patients. Time from infection to symptom onset is commonly between 2 and 14 days, with an average of 5 days. General symptoms are fever, cough, sneezing and shortness of breath. Complications include pneumonia, throat pain and acute respiratory syndrome. Initially, there was no specific treatment or vaccine; efforts consisted of symptom mitigation and supportive

therapy. Recommended preventive measures such as washing the hands with soap, covering the mouth when coughing by using face mask or handkerchief, maintaining one-meter gap from other people and monitoring and self-isolation for 14 days for people who suspect they are infected” [10]. “The disease is diagnosed by using a standard tool of Reverse Transcription Polymerase Chain Reaction (RT-PCR) from a throat swab or nasopharyngeal swab” [11]. “Diagnostic approaches to COVID-19 can be divided into two broad categories, clinical diagnostics and in vitro diagnostics” [12–14]. “Clinical diagnostics for COVID-19 begins with assessment of possibly COVID-19 related symptoms and recent contact and exposure. These should be considered in the context of the SARS-CoV-2 incubation period, which is evaluated to be up to 14 days from exposure, with a median of 4 to 5 days” [15–17]. “In vitro diagnostics for SARS-CoV-2 infection is confirmed by observation of SARS-CoV-2 RNA using NAAT (Nucleic Acid Amplification Test)” [18]. “It usually takes 3.5–4 hours and needs three steps, namely RNA extraction, cDNA synthesis, and amplification and detection of the target nucleic acid, as well as specialized lab equipment” [19]. “Clinical management of SARS relies on supportive care. Broad-spectrum antimicrobial coverage for community obtained pneumonia should be given while virological confirmation is pending. Such antibiotics should be discontinued once the diagnosis of SARS-CoV-2 is confirmed, but nosocomial infections as an outcome of extant intubation and use of corticosteroids should be appropriately managed. The correlation between viral loads and clinical result suggests that suppression of viral replication by effective antiviral agents should be the key to fend off morbidity and mortality” [20-22].

## 2. HISTORY AND LIFE CYCLE OF VIRUS:

### 2.1 History

“The first sufferer of coronaviruses in human present in 1965 by Tyrrell and Bynoe. They noticed that they could isolate a virus named B814. It was noticeable in human embryonic tracheal cell cultures of specimens obtained from the respiratory tract of an adult with common cold symptom. The first sufferers of the present pandemic were seen in Wuhan City of Hubei region China in December 2019, and have been associated to the Huanan Seafood Market at South China, and the infection has spread to many countries around the world” [23].

“SARS is the first known major pandemic disease caused by a coronavirus. During the outbreak in 2003 in which 8,096 cases with 774 deaths had occurred in over 30 countries in 5 continents” [24- 39]. “The disease emerged in late 2002, when an epidemic of acute community acquired atypical pneumonia syndrome was first observed in the Guangdong region. Retrospective surveillance traced several cases of the disease in five cities around Guangzhou over a period of 2 months” [40]. “The index case was announced in Foshan, a city 24 km away from Guangzhou. The second sufferer involved a chef from Heyuan who worked at a restaurant in Shenzhen. The patient had continuous contact with wild game food animals. His wife, two sisters, and seven hospital staff who had contact with him were also affected. From 16 November 2002 to 9 February 2003, a total of 305 cases were reported in mainland China, including 105 health care workers. Next, a devastating outbreak started in Hong Kong Special Administrative Region

(HKSAR), when a professor of nephrology from a teaching hospital in Guangzhou, who had contracted the disease from his patients, came to HKSAR on 21 February 2003. On this day, he transmitted the viral infection to 16 other people in the hotel where he resided. His brother-in-law, one of the secondary sufferers, underwent an open lung biopsy from which the etiological agent was found out and first isolated” [32]. It is a novel coronavirus, named SARS-CoV.

## 2.2 Life cycle with special reference to the molecular mechanism of SARS-CoV-2 infection at the cellular level.

### 2.2.1 Overview of the basic coronavirus component

The coronavirus basically has three components comprising four major proteins and some other accessory proteins with the viral genome at the center. The outermost zone is formed by the club-shaped S (spike) protein jutting out from the virus membrane, and has an appearance reminiscent of the sun’s corona, hence the name of the virus. Then the membrane of the virus carries two membrane proteins, M (for membrane protein) and E (for envelope protein). Thirdly, within the membrane-envelope is the nucleocapsid. The N (for nucleocapsid protein) is the protein component of the viral nucleocapsid and binds to the viral genomic RNA in a “beads-on-a-string” manner. Besides being a structural protein, N protein also contributes to RNA replication and in some cases nuclear localization. The coronavirus RNA is among the largest, if not the largest, RNA in existence. Much of it is taken up for the translation of replicase, a large enzyme complex which expedites the virus genomic replication once it breaks free into the cytoplasm of the host cells. From the remaining genome, the four major structural proteins, S, E, M, N, and, in the particular case of SARS-CoV-2, some eight accessory proteins mostly of uncertain functions. One of these accessory proteins is 3CL<sup>pro</sup> (3-chymotrypsin-like protease, corresponding to nsp5/non-structural protein 5) which self-cleaves the coronavirus’ polyprotein at 11 sites and plays an essential role in the replication of the virus. It is the target of the anti-viral drug nirmatrelvir.

### 2.2.2 Outline of the virus cycle in the cell from entry through replication to exit.

Having entered the newly infected human body, the SARS-CoV-2 virus begins its active life cycle by gaining attachment and entry into the host cell. First, its S protein binds to its specific receptor ACE II (angiotensin conversion enzyme II) expressed on many cells in various organs. Conformational changes then occur in the viral S protein resulting in the emergence of FP (fusion peptide) from the virus membrane. FP is thrust into the host membrane to create a fusion pore. The viral genome then sheds its coating and enters the host cell cytoplasm. This is followed by translation of viral components, using the host endoplasmic reticulum. Assembly of structural viral proteins, S, E, M, take place in the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), while nucleocapsids are formed from the encapsidation of the replication products of viral genome organized by viral replicase and the N protein. All these elements coalesce to form new virions, which are transported to the host cell membrane in Golgi sacs or similar vesicles to exit from the cell and infect other cells. Sometimes, a fraction of S protein might not be assembled into virions but reach the cell surface individually, behaving as membrane protein of the host cell with the potential of binding to the ACE II on another cell,

mediating direct cell-to-cell fusion, infection, and multinucleated giant cell formation. The following sections further illustrate the complex and often confusing steps involved.

### 2.2.3 The S (spike) protein and binding of corona virus to its receptor ACE II.

“The S protein is a trimeric protein, also known as peplomers. It is a class I fusion protein formed from an amino-terminal S1 and a carboxyl-terminal S2 subunits connected by a fusion peptide. The two subunits are indispensable for receptor binding and membrane fusion respectively. S1 is responsible for binding to the ACE II. The receptor binding domain (RBD) of S1 has been mapped to residues 318 to 510” [41- 42]. Conceivably, mutations in this domain will lead to new subtypes of SARS CoV-2 with different infectivity, pathogenicity, resistance to treatment and evasion of host immunity. S1’s binding to the cellular receptor ACE II triggers conformational changes, which re-locate the fusion peptide (FP) upstream of the 2 heptad repeats (HR) of S2 in a transmembrane domain and finally resulting in its insertion into the membrane of the target cell creating a fusion pore between the viral and host cellular lipid membrane barriers. Through the fusion pore the virus genome sheds its coating and enters the cytoplasm of the target cell.

### 2.2.4 Factors facilitating virus entry into host cells.

In order to present the fusion peptide from its original location embedded in the membranous part of the S2 protein two steps are needed. First the subunit S1, after achieving its mission of gaining attachment to its receptor ACE II, has to be cleaved from S2. Next a further part of S2 has to be cleaved to expedite molecular conformational change and bring out the fusion peptide. Subsequent membrane fusion with the target cell could be facilitated by additional proteolytic activity and lower pH (higher acidity).

Much as the key receptor attached by S, the angiotensin-converting enzyme II (ACE II), is also a metalloprotease, it could not effectively cleave S1 from S2 much less further cleaving S2 at its S2’ site. The multiple steps of protein cleavage would still require additional reinforcement. The commonest route of virus entry is direct membrane fusion on the cell surface. The infected cell membrane that is associated with proteases, like factor Xa, or more commonly TMPRSS-2 (transmembrane protease serine type 2), can contribute to S protein cleaving processes especially at S2’ to bring out the fusion protein. This route via the cell membrane is shorter and more direct, and is also the preferred route of membrane fusion by the virus.

If a cell’s membrane has insufficient TMPRSS-2, the virus’ S2 remains intact and it has to settle for a second route of cell entry. Stuck at the cell membrane, it is subjected to endocytosis and then transported into the cytoplasm within the confinement of an endosome i.e. still functionally separated from the cytoplasm. However, within the endosome, the virus’ S2 could be cleaved by cathepsin L under a low pH (acidic) environment.

With either route the ultimate result is to expose the fusion peptide from the membrane remnant of S2 to have it inserted into the cell membrane or the endosome lipid membrane to create a fusion pore and expedite membrane fusion, allowing the viral genome to enter the host cell cytoplasm.

### 2.2.5 Other miscellaneous facts and findings related to viral protein cleavage and cell receptors.

Studies showed that the proteolytic cleavage of SARS CoV can be carried out by the protease Factor Xa and specifically inhibited by a protease inhibitor such as Ben-HCl [43].

#### 2.2.5.b Depletion of ACE II and excess angiotensin II might contribute to organ damage.

“ACE II is expressed in the cells of the lung, intestine, liver, vascular endothelium, heart, testis, and kidney” [44]. “It appears to protect against acute lung injury in a mouse model. The binding of S protein to host cells’ ACE II results in the down-regulation of this enzyme, leaving an excess of its substrate, angiotensin II, unmodified and free to bind to the angiotensin Ia receptor (AT1aR) to aggravate damage in the respective organs. This mechanism may contribute to the severity of lung damage in SARS [45] and COVID-19”.

#### 2.2.5.c The role of Lectin receptors in coronavirus cell entry.

Although the respiratory tract is the major portal of coronavirus entry, yet the well-established virus receptor ACE II is paradoxically under-expressed there. In such situation, the C-type lectin receptors might serve to enhance the ACE II-mediated infection. C-type lectin receptors consist of several types, DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin protein), L-SIGN (liver/lymph-node specific intercellular adhesion molecule-3-grabbing non-integrin protein), and LSECtin (liver sinusoidal endothelial cell lectin). They are able to function as receptor facilitators, having been shown to augment the cellular entry of pseudo type virus expressing S in the scanty presence of ACE II [46-49].

#### 2.2.5.d The role of dendritic cell (DC)

Cells expressing the lectins and with low level or absence of ACE II, like dendritic cells, are able to promote the cell-mediated transfer of SARS-CoV to susceptible cells [46]. Lectins like DC-SIGN may enhance the activity of the scarce available ACE II or simple acts as an alternate receptor. Once infected the dendritic cell may travel to lymph follicles and pass the virus to other cells.

#### 2.2.5.e Endosome route of virus entry, role of cathepsin L and pH, and implication on treatment.

Apart from the virus-preferred route of entry through the cell membrane, the alternative route is by endocytosis. Within the internalized endosome, the proteolytic enzyme cathepsin L and a low pH environment are required for the proteolytic cleavage of S2 protein to bring out the fusion peptide and expedite virus-to-cell fusion. [50-51] This process of viral entry via endosomal endocytosis and membrane fusion within the cytoplasm for the release of viral RNA for translation and replication remains of secondary importance, and attempts to treat COVID-19 with cathepsin L inhibitors, chloroquine and hydroxychloroquine, have generally proved futile. From theoretical consideration such failures are expected as the preferred pathway of membrane fusion by the virus is not via endosomal endocytosis but by direct fusion with the cell membrane aided by the membrane protease TMPRSS-2 (transmembrane serine protease 2).

## 2.2.6 Translation and replication of coronavirus.

“Once within the host cytoplasm, the viral genome assumes its role as a mRNA and translates new viral proteins. Translation begins with the large replicase and two large polyproteins, Orf1a and Orf1ab, that are post-translationally cleaved by the two viral proteases including nsp1 and nsp16. These cleavage products form the replication-transcription complex, which replicates the viral genome and transcribes a 3'-coterminally nested set of 8 sub-genomic RNAs. Therefore, it is conceivable that infected cells contain an increasing number of transcripts- containing genes towards the 3'coterminus of the viral genome. On this basis, Reverse Transcriptase Polymer Chain Reaction (RT-PCR) using the N gene may have a better sensitivity than using the other genes. And other coronaviruses, SARS-CoV may attach by the hydrophobic domains of their replication equipment to the restrict membrane of autophagosomes and form double-membrane vesicles. Once adequate viral genomic RNA and structural proteins are accumulated, viral assembly by budding of the helical nucleocapsid into the ERGIC (endoplasmic reticulum-Golgi intermediate compartment) takes place. At this time, the triple membrane-spanning M protein interacts with N protein and viral RNA to create the basic structure. It interacts with E and S proteins to induce viral budding and release. Unlike other coronaviruses, the M protein of SARS-CoV also implicates another triple-membrane-spanning protein of Orf3a into the virion” [54]. “The N protein is the most copiously expressed viral protein in infected cells in which the mRNA levels were amplified 3 to 10 times, increasing at 12 h post-infection more than other structural genes [55] and therefore a main target for immunohistochemistry and antigen detection in the clinical specimens Various diagnostic tests, antiviral drugs, and vaccines are designed on the basis of our comprehension of the structure and function of the several viral proteins involved in the life cycle of this virus”.

## 3. DIAGNOSIS:

RT-PCR assays are conventional or automated type of assay, with alternative terminologies such as rRT-PCR or RT-qPCR.

“NAAT (Nucleic Acid Amplification Test) is used to detect the presence of viral RNA” [56]. “Purified RNA from clinical specimens is reverse transcribed into complementary DNA (or) cDNA, next added to a master mix containing target primers and fluorophore-quencher probe. The RT-PCR process is carried through in a thermal cycler. The fluorophore-quencher probe is cleaved and creating a fluorescent signal that corresponds to the amplified outcome” [57-58]. “While conventional NAAT start from manual RNA preparation, followed by rRT-PCR, automated systems unsegregate(d) RNA extraction, purification, amplification, detection and outcome in rapid, high-throughput results and decreased contamination [59-62], pre-heating specimens to omit RNA extraction” [63-66]. “Accuracy with alternative, reduced-invasive specimens (e.g., Saliva) in comparison with standard NP specimens has been studied” [67-70]. “Subsequent respiratory specimens may provide information on progress later in the disease course [71], while non-respiratory specimens may correlate with local symptoms (e.g., stool) or clinical seriousness (e.g., blood)” [72-74]. “Swab pooling may increase testing capacity [75]. Various PCR target regions may act on sensitivity” [76-79]. “Other aspects to consider are: Monitoring effect of SARS-CoV-2 genome mutations on RT-PCR showing [80- 81]; First-step

(consolidated RT and PCR) versus Second-step (separate RT and PCR) assays; Uniplex versus Multiplex RT-PCR [82- 83, 58]; Sub-genomic RNA or Ct value as the surrogate for infectivity of live virus” [84].

### 3.1 FUTURE MANAGEMENT:

“Availability of the diagnostic technologies has enabled researchers to quickly adapt them to COVID-19” [58]. “Lessons since the 2002 SARS epidemic have guided development of COVID-19 detection strategies. Only three weeks elapsed since visualization of the virus by using transmission electron microscopy to the elucidation of SARS-CoV-2 genetic sequence, while for SARS-CoV it took five months” [58, 85]. “Control of outbreak requires extensive, ongoing surveillance, and quick sharing of epidemiological data” [86]. “Smartphones are used which increased exponentially including in sub-Saharan Africa, and can be leveraged for this motive as they possess link, computational power, and hardware to ease electronic reporting, epidemiological data basing and sharp end-of-care testing” [58, 87]. “Combining diagnostics tools with smartphone combination could support better management, curb transmission of infection and decrease mortality” [58]. “Safety of laboratory employee who conduct COVID-19 testing is also paramount. Concern for laboratory-associated infection is of specific concern in the setting of individual or personal protective equipment (PPE) shortages, inappropriate microbiological techniques, insufficiency of training, and inadequate detoxification protocols or biosafety measure [88], all of which are more expected to occur when systems are overwhelmed. Optimization of mechanisms to safe-guard laboratory employees should occur in parallel with optimization of COVID-19 diagnostics”.

### 4. PREVENTION:

“To diminished COVID-19 transmission from potentially asymptomatic or pre-symptomatic people, the ECDC (European Centre for Disease prevention and Control) recommends the use of face masks [89], social distancing, travel restrictions on visitors arriving from increasingly high-risk provinces, quarantine for nationals returning from increasingly risk locations, and closure of schools, colleges and certain types of workplaces, the full or partial closure of educational institutions and certain workplaces, restrict the number of visitors and restrict the contact between the residents of confined settings, including prolonged-term care facilities and prisons, cancellation, barring and reduction of mass gatherings and smaller meetings, obligatory quarantine of buildings or residential areas, internal or external boundary closures, and stay-at-home restrictions for whole regions or countries. All ministries should publish(ed) common instructions on COVID-19 prevention and control measures in their organizations” [90]. In April 13, approximately 40,000 tests have been reached per day with a total of 73 authorized laboratories, and the number of daily tests is step by step increasing.

### 5. CONCLUSION

In this review, we conclude that the disease description of COVID-19 is dynamic and continues to quickly evolve. Chest CT has been utilized to aid diagnosis in the absence or doubt of RT-PCR, The development of the lung changes of COVID-19 on CT imaging is also similar to SARS, with the ground-glass and consolidation fare worse or better over several days. This

would be expected, as the 2 infectious agents are part of the coronavirus family. We are only beginning to understand host factors, such as various expression of cell surface proteins that may determine infection risk, disease presentation and results. Unveiling tissue and stage-specific factors contributing to pathology will result in new, effective and disease-specific therapeutic approaches that will control virus replication while restricting inflammatory damage.

#### REFERENCES:

1. Z. Song, Y. Xu, L. Bao, L. Zhang, P. Yu, Y. Qu, et al., From SARS to MERS, thrusting coronaviruses into the spotlight, *Viruses* 11 (1) (2019).
2. C. Drosten, S. Gunther, W. Preiser, S. van der Werf, H.R. Brodt, S. Becker, et al., Identification of a novel coronavirus in patients with severe acute respiratory syndrome, *N. Engl. J. Med.* 348 (20) (2003) 1967–1976.
3. A.M. Zaki, S. van Boheemen, T.M. Bestebroer, A.D. Osterhaus, R.A. Fouchier, Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia, *N. Engl. J. Med.* 367 (19) (2012) 1814–1820.
4. F. Wu, S. Zhao, B. Yu, Y.M. Chen, W. Wang, Z.G. Song, et al., A new coronavirus associated with human respiratory disease in China, *Nature.* 579 (7798) (2020) 265–269.
5. Che, X. Y., B. Di, G. P. Zhao, Y. D. Wang, L. W. Qiu, W. Hao, M. Wang, P. Z. Qin, Y. F. Liu, K. H. Chan, V. C. Cheng, and K. Y. Yuen. 2006. A patient with asymptomatic severe acute respiratory syndrome (SARS) and antigenemia from the 2003–2004 community outbreak of SARS in Guangzhou, China. *Clin. Infect. Dis.* 43:e1–e5.
6. Lau, S. K., P. C. Woo, K. S. Li, Y. Huang, H. W. Tsoi, B. H. Wong, S. S. Wong, S. Y. Leung, K. H. Chan, and K. Y. Yuen. 2005. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. *Proc. Natl. Acad. Sci. USA* 102:14040–14045.
7. Li, W., Z. Shi, M. Yu, W. Ren, C. Smith, J. H. Epstein, H. Wang, G. Crameri, Z. Hu, H. Zhang, J. Zhang, J. McEachern, H. Field, P. Daszak, B. T. Eaton, S. Zhang, and L. F. Wang. 2005. Bats are natural reservoirs of SARS-like coronaviruses. *Science* 310:676–679.
8. Wang, M., M. Yan, H. Xu, W. Liang, B. Kan, B. Zheng, H. Chen, H. Zheng, Y. Xu, E. Zhang, H. Wang, J. Ye, G. Li, M. Li, Z. Cui, Y. F. Liu, R. T. Guo, X. N. Liu, L. H. Zhan, D. H. Zhou, A. Zhao, R. Hai, D. Yu, Y. Guan, and J. Xu. 2005. SARS-CoV infection in a restaurant from palm civet. *Emerg. Infect. Dis.* 11:1860–1865.
9. WHO Q&A on coronaviruses (COVID-19) March 2020, <https://www.who.int/news-room/q-a-detail/q-a-coronaviruses>.

10. Center for disease control and prevention, coronavirus disease 2019 (COVID-19). <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>.
11. Velavan TP, Meyer CG. The COVID-19 epidemic. *Trop Med Int Health*. 2020; 25(3):278–280. doi:10.1111/tmi.13383 <https://pubmed.ncbi.nlm.nih.gov/32052514/>. [CrossRef]
12. Carter LJ, Garner L V, Smoot JW, Li Y, Zhou Q, Saveson CJ, et al. Assay techniques and test development for COVID-19 diagnosis. *ACS Cent Sci*. (2020) 6:591–605. doi: 10.1021/acscentsci.0c00501
13. Cheng MP, Papenburg J, Desjardins M, Kanjilal S, Quach C, Libman M, et al. Diagnostic testing for severe acute respiratory syndrome-related coronavirus 2: a narrative review. *Ann Inter Med*. (2020) 172:726–34. doi: 10.7326/M20-1301
14. Vashist SK. In vitro diagnostic assays for COVID-19: recent advances and emerging trends. *Diagnostics*. (2020) 10:202. doi: 10.3390/diagnostics10040202.
15. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. (2020) 382:1708–20. Doi: 10.1056/NEJMoa2002032.
16. 18. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann Inter Med*. (2020). 172:577–82. Doi: 10.7326/M20-0504.
17. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. (2020) 382:1199–207. Doi: 10.1056/NEJMoa2001316.
18. Alsuliman T, Sulaiman R, Ismail S, Srouf M, Alrstom A. COVID-19 paraclinical diagnostic tools: updates and future trends. *Curr Res Transl Med*. (2020) 68:83–91. Doi: 10.1016/j.retram.2020.06.001.
19. Weissleder R, Lee H, KO J, Pittet MJ. COVID-19 diagnostics in context. *Sci Transl Med*. (2020) 12:eabc1931. Doi: 10.1126/scitranslmed.abc1931.
20. Cinatl, J., B. Morgenstern, G. Bauer, P. Chandra, H. Rabenau, and H. W. Doerr. 2003. Treatment of SARS with human interferons. *Lancet* 362:293–294.
21. Hensley, L. E., L. E. Fritz, P. B. Jahrling, C. L. Karp, J. W. Huggins, and T. W. Geisbert. 2004. Interferon-beta 1a and SARS coronavirus replication. *Emerg. Infect. Dis*. 10:317–319.
22. Tan, E. L., E. E. Ooi, C. Y. Lin, H. C. Tan, A. E. Ling, B. Lim, and L. W. Stanton. 2004. Inhibition of SARS coronavirus infection in

vitro with clinically approved antiviral drugs. *Emerg. Infect. Dis.* 10:581–586.

23. Murphy A, and Bell D.J, et al. COVID-19, Radiopaedia. <https://radiopaedia.org/articles/covid-19-2?lang=us>.
24. Drosten, C., S. Gunther, W. Preiser, S. van der Werf, H. R. Brodt, S. Becker, H. Rabenau, M. Panning, L. Kolesnikova, R. A. Fouchier, A. Berger, A. M. Burguiere, J. Cinatl, M. Eickmann, N. Escriou, K. Grywna, S. Kramme, J. C. Manuguerra, S. Muller, V. Rickerts, M. Sturmer, S. Vieth, H. D. Klenk, A. D. Osterhaus, H. Schmitz, and H. W. Doerr. 2003. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N. Engl. J. Med.* 348:1967–1976.
25. Guan, Y., B. J. Zheng, Y. Q. He, X. L. Liu, Z. X. Zhuang, C. L. Cheung, S. W. Luo, P. H. Li, L. J. Zhang, Y. J. Guan, K. M. Butt, K. L. Wong, K. W. Chan, W. Lim, K. F. Shortridge, K. Y. Yuen, J. S. Peiris, and L. L. Poon. 2003. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science* 302:276–278.
26. Hon, K. L., C. W. Leung, W. T. Cheng, P. K. Chan, W. C. Chu, Y. W. Kwan, A. M. Li, N. C. Fong, P. C. Ng, M. C. Chiu, C. K. Li, J. S. Tam, and T. F. Fok. 2003. Clinical presentations and outcome of severe acute respiratory syndrome in children. *Lancet* 361:1701–1703.
27. Ksiazek, T. G., D. Erdman, C. S. Goldsmith, S. R. Zaki, T. Peret, S. Emery, S. Tong, C. Urbani, J. A. Comer, W. Lim, P. E. Rollin, S. F. Dowell, A. E. Ling, C. D. Humphrey, W. J. Shieh, J. Guarner, C. D. Paddock, P. Rota, B. Fields, J. DeRisi, J. Y. Yang, N. Cox, J. M. Hughes, J. W. LeDuc, W. J. Bellini, and L. J. Anderson. 2003. A novel coronavirus associated with severe acute respiratory syndrome. *N. Engl. J. Med.* 348:1953–1966.
28. Kuiken, T., R. A. Fouchier, M. Schutten, G. F. Rimmelzwaan, G. van Amerongen, D. van Riel, J. D. Laman, T. de Jong, G. van Doornum, W. Lim, A. E. Ling, P. K. Chan, J. S. Tam, M. C. Zambon, R. Gopal, C. Drosten, S. van der Werf, N. Escriou, J. C. Manuguerra, K. Stohr, J. S. Peiris, and A. D. Osterhaus. 2003. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *Lancet* 362:263–270.
29. Lee, N., D. Hui, A. Wu, P. Chan, P. Cameron, G. M. Joynt, A. Ahuja, M. Y. Yung, C. B. Leung, K. F. To, S. F. Lui, C. C. Szeto, S. Chung, and J. J. Sung. 2003. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N. Engl. J. Med.* 348:1986–1994.

30. Marra, M. A., S. J. Jones, C. R. Astell, R. A. Holt, A. Brooks-Wilson, Y. S. Butterfield, J. Khattra, J. K. Asano, S. A. Barber, S. Y. Chan, A. Cloutier, S. M. Coughlin, D. Freeman, N. Girn, O. L. Griffith, S. R. Leach, M. Mayo, H. McDonald, S. B. Montgomery, P. K. Pandoh, A. S. Petrescu, A. G. Robertson, J. E. Schein, A. Siddiqui, D. E. Smailus, J. M. Stott, G. S. Yang, F. Plummer, A. Andonov, H. Artsob, N. Bastien, K. Bernard, T. F. Booth, D. Bowness, M. Czub, M. Drebot, L. Fernando, R. Flick, M. Garbutt, M. Gray, A. Grolla, S. Jones, H. Feldmann, A. Meyers, A. Kabani, Y. Li, S. Normand, U. Stroher, G. A. Tipples, S. Tyler, R. Vogrig, D. Ward, B. Watson, R. C. Brunham, M. Krajdén, M. Petric, D. M. Skowronski, C. Upton, and R. L. Roper. 2003. The genome sequence of the SARS-associated coronavirus. *Science* 300:1399–1404.
31. Nicholls, J. M., L. L. Poon, K. C. Lee, W. F. Ng, S. T. Lai, C. Y. Leung, C. M. Chu, P. K. Hui, K. L. Mak, W. Lim, K. W. Yan, K. H. Chan, N. C. Tsang, Y. Guan, K. Y. Yuen, and J. S. Peiris. 2003. Lung pathology of fatal severe acute respiratory syndrome. *Lancet* 361:1773–1778.
32. Peiris, J. S., S. T. Lai, L. L. Poon, Y. Guan, L. Y. Yam, W. Lim, J. Nicholls, W. K. Yee, W. W. Yan, M. T. Cheung, V. C. Cheng, K. H. Chan, D. N. Tsang, R. W. Yung, T. K. Ng, and K. Y. Yuen. 2003. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 361:1319–1325.
33. Peiris, J. S., K. Y. Yuen, A. D. Osterhaus, and K. Stohr. 2003. The severe acute respiratory syndrome. *N. Engl. J. Med.* 349:2431–2441.
34. Poutanen, S. M., D. E. Low, B. Henry, S. Finkelstein, D. Rose, K. Green, R. Tellier, R. Draker, D. Adachi, M. Ayers, A. K. Chan, D. M. Skowronski, I. Salit, A. E. Simor, A. S. Slutsky, P. W. Doyle, M. Krajdén, M. Petric, R. C. Brunham, and A. J. McGeer. 2003. Identification of severe acute respiratory syndrome in Canada. *N. Engl. J. Med.* 348:1995–2005.
35. Rota, P. A., M. S. Oberste, S. S. Monroe, W. A. Nix, R. Campagnoli, J. P. Icenogle, S. Penaranda, B. Bankamp, K. Maher, M. H. Chen, S. Tong, A. Tamin, L. Lowe, M. Frace, J. L. DeRisi, Q. Chen, D. Wang, D. D. Erdman, T. C. Peret, C. Burns, T. G. Ksiazek, P. E. Rollin, A. Sanchez, S. Liffick, B. Holloway, J. Limor, K. McCaustland, M. Olsen-Rasmussen, R. Fouchier, S. Gunther, A. D. Osterhaus, C. Drosten, M. A. Pallansch, L. J. Anderson, and W. J. Bellini. 2003. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. *Science* 300:1394–1399.
36. Ruan, Y. J., C. L. Wei, A. L. Ee, V. B. Vega, H. Thoreau, S. T. Su, J. M. Chia, P. Ng, K. P. Chiu, L. Lim, T. Zhang, C. K. Peng, E. O. Lin, N. M. Lee, S. L. Yee, L. F. Ng, R. E. Chee, L. W. Stanton, P.

- M. Long, and E. T. Liu. 2003. Comparative full-length genome sequence analysis of 14 SARS coronavirus isolates and common mutations associated with putative origins of infection. *Lancet* 361:1779–1785.
37. So, L. K., A. C. Lau, L. Y. Yam, T. M. Cheung, E. Poon, R. W. Yung, and K. Y. Yuen. 2003. Development of a standard treatment protocol for severe acute respiratory syndrome. *Lancet* 361:1615–1617.
  38. Tsang, K. W., P. L. Ho, G. C. Ooi, W. K. Yee, T. Wang, M. Chan-Yeung, W. K. Lam, W. H. Seto, L. Y. Yam, T. M. Cheung, P. C. Wong, B. Lam, M. S. Ip, J. Chan, K. Y. Yuen, and K. N. Lai. 2003. A cluster of cases of severe acute respiratory syndrome in Hong Kong. *N. Engl. J. Med.* 348:1977–1985.
  39. World Health Organization. 2003. WHO issues consensus document on the epidemiology of SARS. *Wkly. Epidemiol. Rec.* 78:373–375.
  40. Zhong, N. S., B. J. Zheng, Y. M. Li, Poon, Z. H. Xie, K. H. Chan, P. H. Li, S. Y. Tan, Q. Chang, J. P. Xie, X. Q. Liu, J. Xu, D. X. Li, K. Y. Yuen, J. S. Peiris, and Y. Guan. 2003. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. *Lancet* 362:1353–1358.
  41. Babcock, G. J., D. J. Eshaki, W. D. Thomas, Jr., and D. M. Ambrosino. 2004. Amino acids 270 to 510 of the severe acute respiratory syndrome coronavirus spike protein are required for interaction with receptor. *J. Virol.* 78:4552–4560.
  42. Wong, S. K., W. Li, M. J. Moore, H. Choe, and M. Farzan. 2004. A 193-amino acid fragment of the SARS coronavirus S protein efficiently binds angiotensin-converting enzyme 2. *J. Biol. Chem.* 279:3197–3201.
  43. Du, L., R. Y. Kao, Y. Zhou, Y. He, G. Zhao, C. Wong, S. Jiang, K. Y. Yuen, D. Y. Jin, and B. J. Zheng. 2007. Cleavage of spike protein of SARS coronavirus by protease factor Xa is associated with viral infectivity. *Biochem. Biophys. Res. Commun.* 359:174–179.
  44. Hamming, I., W. Timens, M. L. Bulthuis, A. T. Lely, G. J. Navis, and H. van Goor. 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J. Pathol.* 203:631–637.
  45. Kuba, K., Y. Imai, S. Rao, H. Gao, F. Guo, B. Guan, Y. Huan, P. Yang, Y. Zhang, W. Deng, L. Bao, B. Zhang, G. Liu, Z. Wang, M. Chappell, Y. Liu, D. Zheng, A. Leibbrandt, T. Wada, A. S. Slutsky, D. Liu, C. Qin, C. Jiang, and J. M. Penninger. 2005. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat. Med.* 11:875–879.

46. Chan, V. S., K. Y. Chan, Y. Chen, L. L. Poon, A. N. Cheung, B. Zheng, K. H. Chan, W. Mak, H. Y. Ngan, X. Xu, G. Screaton, P. K. Tam, J. M. Austyn, L. C. Chan, S. P. Yip, M. Peiris, U. S. Khoo, and C. L. Lin. 2006. Homozygous L-SIGN (CLEC4M) plays a protective role in SARS coronavirus infection. *Nat. Genet.* 38:38–46.
47. Gramberg, T., H. Hofmann, P. Moller, P. F. Lalor, A. Marzi, M. Geier, M. Krumbiegel, T. Winkler, F. Kirchhoff, D. H. Adams, S. Becker, J. Munch, and S. Pohlmann. 2005. LSECTin interacts with filovirus glycoproteins and the spike protein of SARS coronavirus. *Virology* 340:224–236.
48. Jeffers, S. A., S. M. Tusell, L. Gillim-Ross, E. M. Hemmila, J. E. Achenbach, G. J. Babcock, W. D. Thomas, Jr., L. B. Thackray, M. D. Young, R. J. Mason, D. M. Ambrosino, D. E. Wentworth, J. C. Demartini, and K. V. Holmes. 2004. CD209L (L-SIGN) is a receptor for severe acute respiratory syndrome coronavirus. *Proc. Natl. Acad. Sci. USA* 101:15748–15753.
49. Yang, Z. Y., Y. Huang, L. Ganesh, K. Leung, W. P. Kong, O. Schwartz, K. Subbarao, and G. J. Nabel. 2004. pH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced by dendritic cell transfer through DC-SIGN. *J. Virol.* 78:5642–5650.
50. Huang, I. C., B. J. Bosch, F. Li, W. Li, K. H. Lee, S. Ghiran, N. Vasilieva, T. S. Dermody, S. C. Harrison, P. R. Dormitzer, M. Farzan, P. J. Rottier, and H. Choe. 2006. SARS coronavirus, but not human coronavirus NL63, utilizes cathepsin L to infect ACE2-expressing cells. *J. Biol. Chem.* 281: 3198–3203.
51. Simmons, G., D. N. Gosalia, A. J. Rennekamp, J. D. Reeves, S. L. Diamond, and P. Bates. 2005. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. *Proc. Natl. Acad. Sci. USA* 102:11876–11881.
52. Keyaerts, E., L. Vijgen, P. Maes, J. Neyts, and M. Van Ranst. 2004. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochem. Biophys. Res. Commun.* 323:264–268.
53. Vincent, M. J., E. Bergeron, S. Benjannet, B. R. Erickson, P. E. Rollin, T. G. Ksiazek, N. G. Seidah, and S. T. Nichol. 2005. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Viol. J.* 2:69.
54. Ito, N., E. C. Mossel, K. Narayanan, V. L. Popov, C. Huang, T. Inoue, C. J. Peters, and S. Makino. 2005. Severe acute respiratory syndrome coronavirus 3a protein is a viral structural protein. *J. Virol.* 79:3182–3186.
55. Hiscox, J. A., D. Cavanagh, and P. Britton. 1995. Quantification of individual subgenomic mRNA species during replication of the

- coronavirus transmissible gastroenteritis virus. *Virus Res.* 36:119–130.
56. Alsuliman T, Sulaiman R, Ismail S, Srouf M, Alrstom A. COVID-19 paraclinical diagnostic tools: updates and future trends. *Curr Res Transl Med.* (2020) 68:83–91. doi: 10.1016/j.retram.2020.06.001
  57. Premraj A, Aleyas AG, Nautiyal B, Rasool TJ. Nucleic acid and immunological diagnostics for SARS-CoV-2: processes, platforms and pitfalls. *Diagnostics.* (2020) 10:866. doi: 10.20944/preprints202009.0526.v1
  58. Udugama B, Kadhiresan P, Kozłowski HN, Malekjahani A, Osborne M, Li VYC, et al. Diagnosing COVID-19: the disease and tools for detection. *ACS Nano.* (2020) 14:3822–35. doi: 10.1021/acsnano.0c02624
  59. Pfefferle S, Reucher S, Nörz D, Lütgehetmann M. Evaluation of a quantitative RT-PCR assay for the detection of the emerging coronavirus SARS-CoV2 using a high throughput system. *Euro Surveill.* (2020) 25:2000152. doi: 10.2807/1560-7917.ES.2020.25.9.2000152
  60. Craney AR, Velu PD, Satlin MJ, Fauntleroy KA, Callan K, Robertson A, et al. Comparison of two high-throughput reverse transcription-PCR systems for the detection of severe acute respiratory syndrome coronavirus 2. *J Clin Microbiol.* (2020) 58:e00890–20. doi: 10.1128/JCM.00890-20
  61. U. S. Food and Drug Administration. In Vitro Diagnostics EUAs - Molecular Diagnostic Tests for SARS-CoV-2. (2021). Available online at: <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-molecular-diagnostic-tests-sars-cov-2>
  62. Poljak M, Korva M, Knap Gašper N, Fujs Komloš K, Sagadin M, Uršic T, et al. Clinical evaluation of the cobas SARS-CoV-2 test and a diagnostic platform switch during 48 hours in the midst of the COVID-19 pandemic. *J Clin Microbiol.* (2020) 58:e00599–20. doi: 10.1128/JCM.00599-20
  63. Alcoba-Florez J, González-Montelongo R, Íñigo-Campos A, de Artola DGM, Gil-Campesino H, The Microbiology Technical Support Team, et al. Fast SARS-CoV-2 detection by RT-qPCR in preheated nasopharyngeal swab samples. *Int J Infect Dis.* (2020) 97:66–8. doi: 10.1016/j.ijid.2020.05.099
  64. da Silva SJR, Silva CTA da, Guarines KM, Mendes RPG, Pardee K, Kohl A, et al. Clinical and laboratory diagnosis of SARS-CoV2, the virus causing COVID-19. *ACS Infect Dis.* (2020) 6:2319–36. doi: 10.1021/acsinfecdis.0c00274

65. Fomsgaard AS, Rosenstjerne MW. An alternative workflow for molecular detection of SARS-CoV-2 - escape from the NA extraction kit-shortage, Copenhagen, Denmark, March 2020. *Eurosurveillance*. (2020) 25:2000398. doi: 10.2807/1560-7917.ES.2020.25.14.2000398
66. Lübke N, Senff T, Scherger S, Hauka S, André M, Adams O, et al. Extraction-free SARS-CoV-2 detection by rapid RT-qPCR universal for all primary respiratory materials. *J Clin Virol*. (2020) 132:104579. doi: 10.1016/j.jcv.2020.104579
67. Péré H, Podglajen I, Wack M, Flamarion E, Mirault T, Goudot G, et al. Nasal Swab sampling for SARS-CoV-2: a convenient alternative in times of nasopharyngeal swab shortage. *J Clin Microbiol*. (2020) 58:e00721–20. doi: 10.1128/JCM.00721-20
68. McCulloch DJ, Kim AE, Wilcox NC, Logue JK, Greninger AL, Englund JA, et al. Comparison of unsupervised home self-collected midnasal swabs with clinician-collected nasopharyngeal swabs for detection of SARS-CoV-2 infection. *JAMA Netw Open*. (2020) 3:e2016382. doi: 10.1001/jamanetworkopen.2020.16382 .
69. To KKW, Tsang OTY, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV2: an observational cohort study. *Lancet Infect Dis*. (2020) 20:565–74. doi: 10.1016/S1473-3099(20)30196-1
70. Azzi L, Carcano G, Gianfagna F, Grossi P, Gasperina DD, Genoni A, et al. Saliva is a reliable tool to detect SARS-CoV-2. *J Infect*. (2020) 81:e45–50. doi: 10.1016/j.jinf.2020.04.005
71. Martinez RM. Clinical samples for SARS-CoV-2 detection: review of the early literature. *Clin Microbiol Newslett*. (2020) 42:121–7. doi: 10.1016/j.clinmicnews.2020.07.001
72. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARSCoV-2 in different types of clinical specimens. *JAMA*. (2020) 323:1843–4. doi: 10.1001/jama.2020.3786
73. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe*. (2021) 2:e13–22. doi: 10.1016/S2666-5247(20)30172-5
74. Khoury NC, Russi TJ. A case of gastrointestinal-predominant COVID19 demonstrates value of stool PCR test. *J Med Virol*. (2021) 93:662–3. doi: 10.1002/jmv.26448
75. Abdalhamid B, Bilder CR, Mccutchen EL, Hinrichs SH, Koepsell SA, Iwen PC. Assessment of specimen pooling to conserve SARS

- CoV-2 testing resources. *Am J Clin Pathol.* (2020) 153:715–8. doi: 10.1101/2020.04.03.20050195
76. Matsumura Y, Shimizu T, Noguchi T, Nakano S, Yamamoto M, Nagao M. Comparison of 12 molecular detection assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *J Mol Diagn.* (2021) 23:164–70. doi: 10.1016/j.jmoldx.2020.11.007
  77. Vogels CBF, Brito AF, Wyllie AL, Fauver JR, Ott IM, Kalinich CC, et al. Analytical sensitivity and efficiency comparisons of SARS-CoV2 RT-qPCR primer-probe sets. *Nat Microbiol.* (2020) 5:1299–305. doi: 10.1038/s41564-020-0761-6.
  78. Nalla AK, Casto AM, Huang M-LW, Perchetti GA, Sampoleo R, Shrestha L, et al. Comparative performance of SARS-CoV-2 detection assays using seven different primer-probe sets and one assay kit. *J Clin Microbiol.* (2020) 58:e00557–20. doi: 10.1128/JCM.00557-20.
  79. van Kasteren PB, van der Veer B, van den Brink S, Wijsman L, de Jonge J, van den Brandt A, et al. Comparison of seven commercial RT-PCR diagnostic kits for COVID-19. *J Clin Virol.* (2020) 128:104412. doi: 10.1016/j.jcv.2020.104412.
  80. Artesi M, Bontems S, Göbbels P, Franckh M, Maes P, Boreux R, et al. A recurrent mutation at position 26340 of SARS-CoV-2 is associated with failure of the E gene quantitative reverse transcription-PCR utilized in a commercial dual-target diagnostic assay. *J Clin Microbiol.* (2020) 58:e01598–20. doi: 10.1128/JCM.01598-20.
  81. Galloway SE, Paul P, MacCannell DR, Johansson MA, Brooks JT, MacNeil A, et al. Emergence of SARS-CoV-2 b. 1.1. 7 lineage—United States, December 29, 2020–January 12, 2021. *Morb Mortal Wkly Rep.* (2021) 70:95. doi: 10.15585/mmwr.mm7003e2.
  82. Premraj A, Aleyas AG, Nautiyal B, Rasool TJ. Nucleic acid and immunological diagnostics for SARS-CoV-2: processes, platforms and pitfalls. *Diagnostics.* (2020) 10:866. doi: 10.20944/preprints202009.0526.v1.
  83. Afzal A. Molecular diagnostic technologies for COVID-19: limitations and challenges. *J Adv Res.* (2020) 26:149–59. doi: 10.1016/j.jare.2020.08.002.
  84. Bullard J, Dust K, Funk D, Strong JE, Garnett L, Boodman C, et al. Predicting infectious SARS-CoV-2 from diagnostic samples. *Clin Infect Dis.* (2020) 71:2663–6. doi: 10.1093/cid/ciaa638.
  85. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for

- disease control and prevention. *JAMA*. (2020) 323:1239–42. doi: 10.1001/jama.2020.2648
86. Smith RD. Responding to global infectious disease outbreaks: lessons from SARS on the role of risk perception, communication and management. *Soc Sci Med*. (2006) 63:3113–23. doi: 10.1016/j.socscimed.2006.08.004
87. Wood CS, Thomas MR, Budd J, Mashamba-Thompson TP, Herbst K, Pillay D, et al. Taking connected mobile-health diagnostics of infectious diseases to the field. *Nature*. (2019) 566:467–74. doi: 10.1038/s41586-019-0956-2
88. Karthik K, Aravindh Babu RP, Dhama K, Chitra MA, Kalaiselvi G, Alagesan Senthilkumar TM, et al. Biosafety Concerns during the collection, transportation, and processing of COVID-19 samples for diagnosis. *Arch Med Res*. (2020) 51:623–30. doi: 10.1016/j.arcmed.2020.08.007
89. European Centers for Disease Control (ECDC) (2020). Using face masks in the community reducing COVID-19 transmission from potentially asymptomatic or presymptomatic people through the use of face masks ECDC Technical Report [online]. Website <https://www.ecdc.europa.eu/en/publications-data/using-face-masks-communityreducing-covid-19-transmission> [accessed 8 April 2020].
90. T.C. Sağlık Bakanlığı (2020). Kurumlar İçin Alınan Kararlar [online]. Website <https://covid19bilgi.saglik.gov.tr/tr/alinankaralar.htm> [accessed 13 April 2020].