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Lab-on-paper based devices for COVID-19 sensors

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2.1 Introduction

In December 2019, a disease linked to the coronavirus (CoV) was identified in the capital of China's Wuhan [1]. When seen under an electron microscope, CoVs, which are enveloped positive-sense RNA viruses, appear like crown-shaped viruses. There are four subtypes of CoVs such as (a) alpha, (b) beta, (c) delta and, (d) gamma CoV. Coronavirus disease is caused by the extreme acute respiratory syndrome coronavirus 2, which is caused by a beta coronavirus (-CoVs or Beta-CoVs) (SARS-CoV-2). Infected people may have a fever of 38° C, cough, and shortness of breath [2]. WHO officially called COVID-19, an abbreviated form of coronavirus disease 2019, on February 12, 2020. The original name for the virus was 2019-nCoV that caused the COVID-19 pneumonia epidemic. Coronavirus, which resembles SARS (bat-SL-CoVZC45 and bat-SL-CoVZXC21) and was later renamed severe acute respiratory syndrome coronavirus-2, or SARS-CoV-2, owing to its close genetic relation (88% similarity) with two bat-originated viruses. Besides that, the SARS-CoV-2 has a genetic resemblance of 79% to SARS-CoV and 50% to the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [3]. COVID-19 was declared a pandemic by the WHO on March 11, 2020, indicating a significant risk of global contamination and the need for precautions. Droplets and direct contact are the leading modes of SARS-CoV-2 transmission among humans, as per reports from affected countries [4]. Relevant genes for viral replication, nucleocapsid formation, and spike formation are located in the ORF1 downstream regions of all coronaviruses. The coronavirus's outer surface

glycoprotein spikes are responsible for the virus's attachment and entrance into host cells. The virus can infect many hosts because its RBD, that is, the receptor-binding domain is roughly connected. Coronavirus's entry mechanism is dependent upon cellular proteases such as-human airway trypsin-like protease (HAT), cathepsins, and transmembrane protease serine 2 (TMPRSS2), which split the spike protein and trigger more penetration changes. SARS-CoV-2 has the classic coronavirus structure with spike protein and also expresses RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins, among other polyprotein, nucleoproteins, and membrane proteins [5]. To maintain van der Waals forces, the SARS-CoV-2 spike protein has a three-dimensional structure in the receptor-binding domain.

2.1.1 Life cycle of SARS-CoV-2

As the S protein binds to the cellular receptor ACE2, SARS-CoV-2 begins its life cycle in host cells [6]. After receptor binding, the conformation change in the S protein induces viral envelope fusion with the cell membrane via an endosomal pathway. The SARS-CoV-2 then injects RNA into the host cell. Pp1a and 1ab are viral replicase polyproteins that are encoded into genome RNA and then cleaved into small products by viral proteinases. The polymerase produces a sequence of subgenomic mRNAs, which are then converted into viral proteins, using the discontinuous transcription. Virions are formed in the endoplasmic reticulum and Golgi by combining viral proteins and genome RNA, which are then transferred by vesicles and released from the cell [7]. Diagrammatic representation of SARS-CoV-2 life cycle is shown in Fig. 2.1.

Coronavirus has a high transmitting ability which makes it impossible to deter and control [8]. Since there is no clear vaccine/antiviral therapy for coronavirus, it is important to get a diagnosis as soon as possible to decrease the chance of severe difficulties and mortality [9]. When it comes to detection techniques, the whole world depends on a single conventional tool, that is, RT-PCR, this diagnostic test gives various benefits like-reproducibility, accuracy, sensitivity and it detect the virus at the initial stage and can be used on weak immunity patients, although it has disadvantages in that it takes experience and is expensive due to the cumbersome instrument used. One significant disadvantage of this approach is that diverse temperature is needed for diverse reaction cycles, which make it challenging to use at the point-of-care (POC). As a result, POC instruments for on-site diagnosis have become increasingly important [10]. Improvements in POC diagnosis, chip- or paper-based biosensors have been established for quick analysis of transmittable infections. Based on colorimetric, fluorescent, or electrochemical identification methods, they are commonly used to identify- nucleic acids, antibodies/antigens, in basic samples like- blood, saliva and, sputum. They have a variety of benefits,

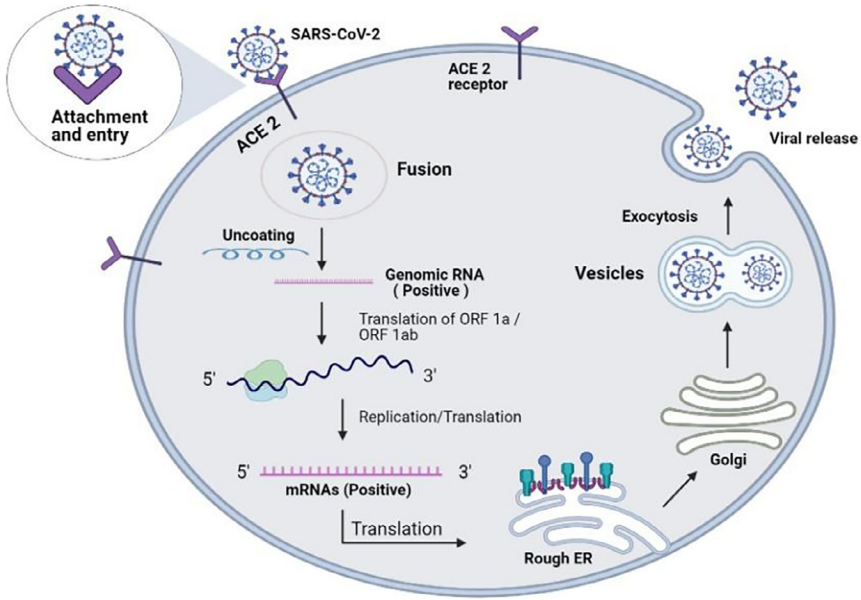


FIGURE 2.1 Entry of SARS-CoV2 inside the cell through receptor, translation, and replication of virus inside the cell, the release of viral components through exocytosis to infect the other cells.

including being cost-effective, responsive, and precise, accessible, fast and durable, less instruments and deliverable to end-users (ASSURED). The outcome can be achieved quickly and easily, allowing for quick decision-making and reducing the chance of human-to-human transmission [11]. The most recent developments in POC biosensors to detect coronavirus are reviewed in this chapter, along with the benefits of lab-on-chip biosensors are also discussed, as well as the commercially available COVID-19 lab-on-chip biosensors. Fig. 2.2 represents the different diagnosis approaches to detect COVID-19 infection.

2.2 LOC biosensor (overview and fabrication)

Amid all analytical methods, the biosensor was confirmed as one of the progressive systems [12]. A biosensor is a bioanalytical instrument that contains a recognition feature as well as a transducing device. The word “biosensor” refers to a common diagnostic method that consists of biocomponents like protein, enzyme, antibody, and so on. Clark and Lyons invented the first biosensor in 1962 [13]. Since then, there has been incredible progress in both science and biosensor use, including emerging technologies including bioelectronics/ electrochemistry and nanotechnology. A

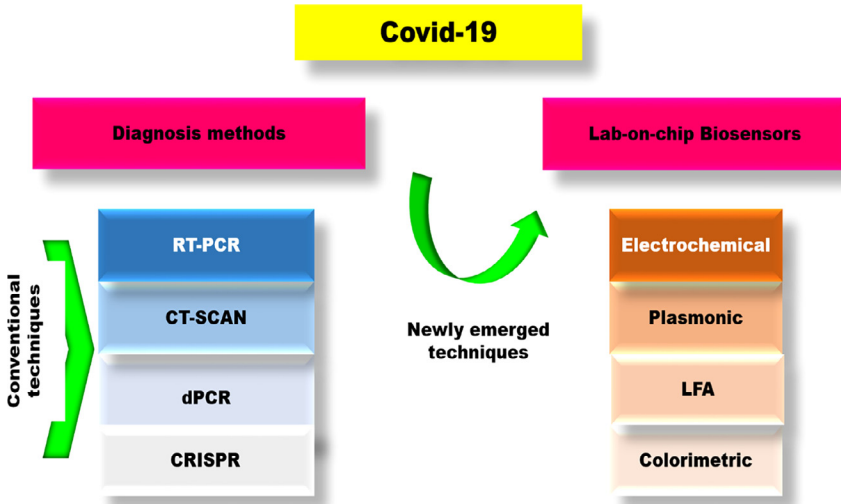


FIGURE 2.2 Different diagnosis approaches of COVID-19.

biosensor is made up of three parts: a recognizing unit, a signal transducer, and a signal amplifier that transmits and demonstrates the data. The recognition element identifies a signal from the surroundings in an analyte form, which is then converted to a measured electric output by the transducer [14]. A well-defined COVID-19 biosensor along with its components is represented in Fig. 2.3. Biosensors should be thought of as an innovative diagnostic instrument with all of the advantages of high sensitivity, accuracy, and low volume. Biology and electronics are combined to make the system more available, digital, and to create a small-scale multiplexed system [15].

Biosensors' enormous promise in medical diagnostics has prompted researchers to evolve this technology and develop novel techniques over time. The popularity of biosensors in medical diagnostics is focused on their ability to identify a wide variety of biomolecules. However, meeting efficiency demands while maintaining simplicity and affordability remains a significant challenge. The ultimate aim is to bring POC research to remote areas around the world, especially in developed countries. It involves continuous technological advancements in multiplexing, fabrication, and miniaturization of biosensor instruments in order to provide lab-on-chip-diagnosis systems to the public [16]. Lab-on-chip technology refers to approaches that conduct numerous laboratory activities on a small scale like-preparation of chemicals and analysis which helps it to make a handheld and portable instrument. To put it another way, a lab-on-chip is a method for scaling one or many laboratory operations down to chip size. This chip can be anything from a few millimeters to a few square centimeters

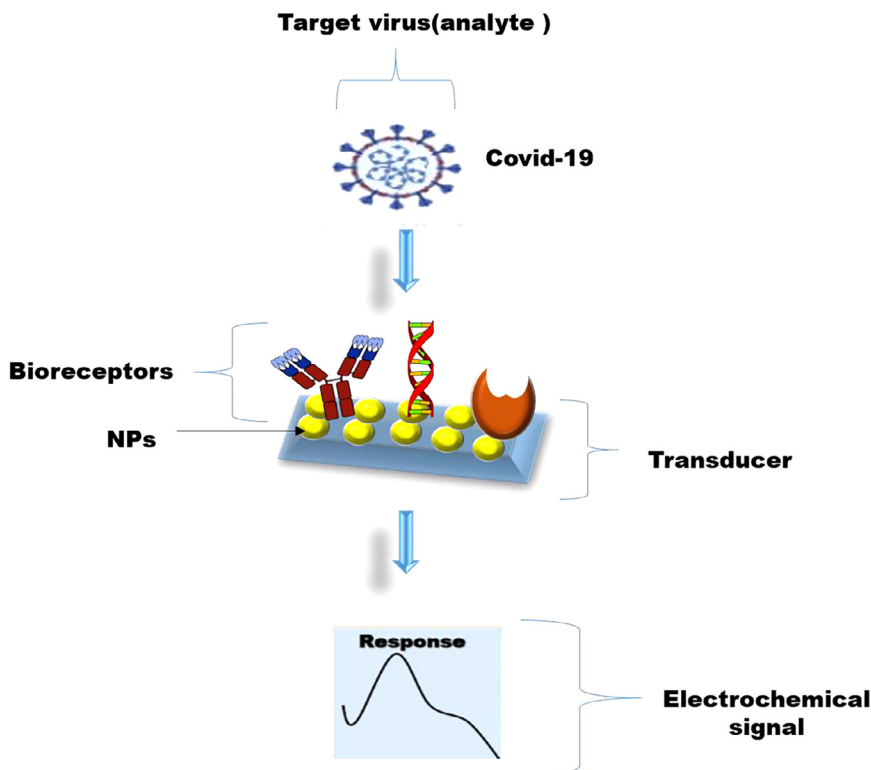


FIGURE 2.3 Diagrammatic representation of COVID-19 biosensor.

in size. The fusion of fluidics, circuitry, optics, and biosensors is known as LOC [17]. Compactness, portability, modularity, reconfigurability, integrated computing, automatic sample handling, low electronic noise, minimal power consumption, and simple component integration are some of the noteworthy technological advantages of lab-on-chip systems. Besides that, lab-on-chip systems can accommodate a broad variety of processes, including sampling, routing, transport, dispensing, and combining, with less moving or rotating parts, extending the device's flexibility and lifetime [18].

2.3 LOC fabrication

Micro and nanoscale LOC applications have been made possible thanks to advancements in microfluidic and microfabrication processes. Based on the liquid propulsion concept, microfluidic-LOC systems are divided

into five categories: (a) capillary, (b) pressure-driven, (c) centrifugal, (d) acoustic-driven, and (e) electrokinetic. Various fabrication approaches are used to make lab-on-chip-based devices by using different materials such as polymeric, glass, and, silicon [19]. Similarly, there are numerous fabrication approaches for LOC and paper-based microfluidic tools like wax printing, alkyl ketene dimer (AKD) printing, flexographic printing, and layer-by-layer 3D affixing, polydimethylsiloxane (PDMS) plotting, wax/inkjet/wax screen printing, wax dipping, plasma treatment, photolithography, deposition, etching, and lift-off lithography [20]. Moreover, a patterning method called soft-lithography is mainly considered for soft materials such as PDMS, Replica molding, microcontact printing, and microtransfer molding are all examples of soft lithography [21]. However, metal lift-off lithography has been generally used for patterning noble metal thin films like- gold, silver, tantalum, nickel, or iron, which are tough to be imprinted by traditional techniques [22]. Another technique used in the fabrication is the screen printing technique. In Fig. 2.4 printing method is described. This method utilizes carbon conductive ink as a substrate.

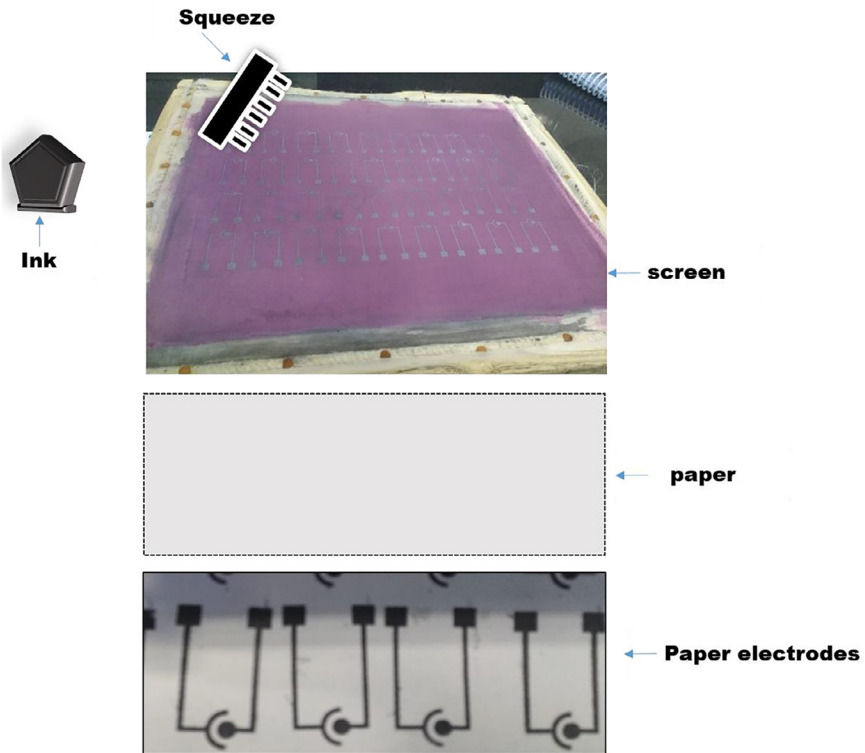


FIGURE 2.4 Fabrication method of lab on chip based biosensor to detect COVID-19.

TABLE 2.1 LOC fabrication materials and methods [12,23,25].

Materials	Techniques of fabrication
Polyurethane	Soft lithography
Polydimethylsiloxane	Soft lithography
Poly(methyl methacrylate)	Simple hot embossing method.
Surface oxidized silicon	Chemical dry etching
Glass	Isotropic wet etching and chemical dry etching
Paper	Screen printing

TABLE 2.2 Commercially available primers/probe of SARS CoV-2.

Gene target	Primer/probe	Sequences (5'-3')	Developed by	Reference
RdRp	nCoV IP2 Fw	ATGAGCTTAGTCCTGTTG	Institut Pasteur	[22]
	nCoV IP2 Rv	CTCCCTTTGTTGTGTTGT		
	IP2 probe	HEX ^{HEX} AGATGCTCTGTGCTGCCGGTA ^{BHQ1}		

Carbon conductive ink was squeezed on the screen so that the electrodes were imprinted on the surface of the paper [23]. Table 2.1 represents the fabrication methods along with their materials.

2.4 Conventional method to detect COVID-19

2.4.1 Reverse transcription-PCR

Conventionally, this is a gold standard approach to detect coronavirus [26]. To identify the virus, this molecular detection method evaluates the nucleic acids found in the sample. Real-time RT-PCR reaction is the most widely utilized laboratory identification tool for the clinical detection of viral diseases, like- SARS-CoV and MERS-CoV, which have been diagnosed and monitored using the same technique. Commercially available primers and probes of SARS-CoV-2 for RT-PCR are mentioned in Table 2.2 [27].

2.4.2 Digital PCR (dPCR)

Vogelstein and Kinzler were the first to mention the term “dPCR” in 1999 [29]. The principle of this technique, before amplification its partition the mixture of PCR into various independent subreactions to analyze the original target molecule’s numbers by calculating the partitions which

show the PCR results (+ve and -ve) and after amplification it determines the Poisson distribution. Commonly, this method can be divided into two terms like- (a) chip-based dPCR (b) droplet-based dPCR [30]. This digital PCR is also suitable for the diagnosis of coronavirus, like- [31] and [32] utilizes d-polymerase chain reaction in context with SARS-CoV-2.

2.4.3 CT-SCAN

This technique is more trustworthy, convenient and faster to classify and assess COVID-19 as compared to PCR. Thorax computer tomography can be used at the initial stage of COVID-19 patients because it is present in almost every clinic. The essential point seen in the images of CT scan is- crazy paving pattern, ground-glass opacities, reticular pattern, and consolidation in COVID-19 patients [33]. Zhao et al. demonstrated the association between the CT-scan outcomes and the medical situations of coronavirus by collecting the data of 101 COVID-19 pneumonia cases from Hunan, China. After collecting, detailing of all the basic imaging features is compared and assessed [34].

2.4.4 CRISPR-based technologies

This method offers an attractive opportunity to permit good alternatives or development to detect COVID-19 by providing a sensitive, specific, and speedy assay. This technique mainly involved the CRISPER-Cas system which used proteins as CRISPR effectors named Cas12/cas13. In this assay these proteins play a very crucial role, which helps in COVID-19 detection [35]. Currently, many researchers used these methods like- Lucia C et al., which stated this CRISPR-Cas 12 assay to diagnose synthetic SARS-Cov-2 RNA sequence [36] (Table 2.3), which comprises all the conventional methods along with their disadvantages.

As a result of the aforementioned drawbacks, these methods are ineffective in situations requiring rapid screening in populated areas where large quantities of samples must be checked.

2.5 Lab-on-chip based biosensors to detect COVID-19

2.5.1 Electrochemical biosensor

Basically, in this device electrochemically transducer is involved along with electrodes that are chemically modified, and the material was used either semiconducting or conducting which is mainly coated with a bio-chemical film [42]. This device is one of the novel techniques to detect viral antigens/nucleic acids. This electrochemical biosensor mainly focuses on

TABLE 2.3 Limitations of conventional methods.

Conventional methods	Limitations	References
RT-PCR	Requires qualified and educated personnel, as well as facilities, and results take at least 6–24 hours.	[37]
CT-SCAN	Costly, exposes patients to a high dose of radiation, and may be confused, leading to disease-mismanagement.	[38]
dPCR	The major drawbacks of using digital PCR to reliably measuring the proviral DNA or RNA reservoir are false positive results. dPCR assays may be to blame for the sensitivity limitations and cost is high.	[40]
CRISPR	Specificity is very low and a poor selection of delivery tools is all factors that limit its ability to reach its full potential.	[41]

providing a point of care testing (POCT) to the users. There are so many advantages of electrochemical biosensor over conventional as it is cheap, easy to handle, and have time-saving testing. In this current pandemic, this device is really becoming a challenge to detect COVID-19 as it gives a patient –ve or +ve results within minutes or one hour [43]. Many scientists from all over the world used electrochemical biosensors to detect COVID-19 and to make them economically good such as Alafeef et al. used paper in electrochemical biosensor chips to diagnose genetic material SARS-CoV-2 digitally in very little time, that is, 5 minutes. This research is concluded that this paper-based electrochemical chip biosensor is very inexpensive, easily handle, and assessable [44]. To make this testing more advanced Zhao et al. used a smartphone for the detection of SARS-CoV-2 RNA. In this, the author used a super-sandwich type electrochemical biosensor and utilizes calixarene-functionalized GO and the outcome ratios are higher while compare to RT-qPCR, which makes it ultrasensitive testing. In this, author used calixarene-functionalized graphene oxide [45], however, there are so many functionalized materials is used by many authors like-Vadlamani et al. used cobalt-functionalized titanium dioxide nanotubes in an electrochemical biosensor to detect S-receptor binding domain protein (SARS-CoV-2) [46]. To make their research effective and unique scientists try to do new experiments by using different materials and combined with electrochemical biosensors such as Fabiani et al. coupled the magnetic beads with screen printed electrodes which are based on carbon black nanomaterials in an electrochemical immunoassay to detect SARS-CoV-2 (S/N proteins) in the patient saliva [47]. While another author, Chai bun et al. describes an electrochemical biosensor to detect SARS-CoV-2 based on isothermal RCA that is, rolling circle amplification later the amplicons

of RCA are hybridized by using probes and functionalized via redox-active labels which can be easily detectable [48]. On the other hand, Funari et al. built an optomicrofluidic chip-based electrochemical biosensor by utilizing gold nano spike for detected antibodies of SARS-CoV-2 spike protein [49].

2.5.2 Plasmonic biosensor

Plasmonic biosensing is one of those methods that have the ability to detect the sample at very low concentrations. In this method, label-free diagnosis of bioanalytical targets can be done in context with a point of care testing [50]. Plasmonic biosensor is also known as SPR that is, surface plasmonic resonance. This device can become an indispensable instrument in the field of medical sciences, which can also be used to diagnose COVID-19 [51]. Using SPR biosensing technology, Masson's research group recently announced the use of human serum samples without dilution for the detection of nucleocapsid antibodies specific for SARS-CoV-2 [52]. This SPR-based sensor was recently identified for detecting nucleocapsid antibodies specific for SARS-CoV-2 in undiluted human serum rather than oropharyngeal swab. Anti-SARS-CoV-2 antibodies were detected in the nM range using an SPR sensor coated with a peptide monolayer and functionalized with SARS-CoV-2 nucleocapsid recombinant protein. As a result, this bioassay is fast and label-free, and it can diagnose samples in as little as 15 minutes after sample or sensor touch [53]. Many scientists work on this plasmonic biosensor to detect COVID-19 as it gives numerous advantages as compared to the RT-PCR such as Peng X et al. developed a near-infrared region plasmonic biosensor to detect SARS-CoV-2 along with their S protein and integrated with a telluride-MOS₂ layer with transparent indium tin oxide, which shows great results in term of identification and capturing that helps to detect SARS-CoV-2 and S protein [54]. A plasmonic biosensor is also improved by coupling this biosensor with other methods like Qiu et al., combining these two methods—plasmonic photothermal and localized surface plasmon resonance and term as—dual-functional plasmonic biosensor. The sensitivity is increased by utilizing 2D gold Nis that is, nanoislands, and thermoplasmonic heating is done for better results which makes it a novel technique [55]. Pig sera were used by Bong JH et al. to purify antibodies against Coronavirus 2 nucleoprotein (NP) (SARS-CoV-2). After isolation of the antibody fraction using a protein-A axis, the final yield of purified antibodies against SARS-CoV-2 NPs from 1 mL of pig sera was determined to be 0.26–0.05% (absolute total of 143.4 25.2 ng, n = 5). The binding processes of the isolated antibodies were tested using immunoassay and immune-staining. An SPR biosensor with isolated antibodies against SARS-CoV-2 NPs was used to detect SARS-CoV-2, MERS-CoV, and CoV strain 229E in the culture fluid [56].

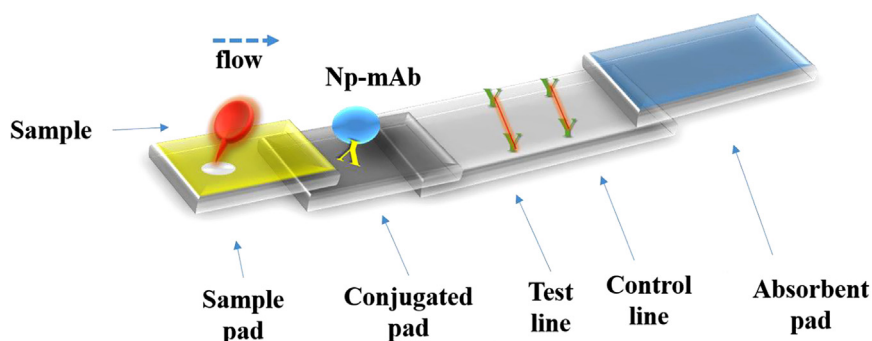


FIGURE 2.5 Diagrammatic representation of lateral flow.

2.5.3 Lateral flow assay (LFA) principle

In 1956, the first time detection (semiquantitative) of glucose in the urine is done by the paper device. One of the popular applications of LFA is the pregnancy kit [57].

Lateral flow tests (LFTs) are an example of a tool that can be used without any special equipment, expertise, or experience [58]. The LFAs/LFTS are well-known POC instruments that have recently emerged as the most striking tools for qualitative, semiquantitative, and even quantitative identification of multiple analytes, particularly biomarkers. The World Health Organization's (WHO) ASSURED guidelines stipulate that all POC devices must meet certain requirements, including being (a) affordable, (b) sensitive, (c) specific, (d) user-friendly, (e) rapid and durable, (f) equipment-free, and (g) delivered to end-users [59]. The cost-effectiveness is achieved primarily by the use of cellulosic materials and plastic supports. Simple process and result explanation, on the other hand, satisfy the requirements of the end-user. Lateral flow assay is very easy for the users. The main protocol to perform this assay is done by adding the sample on the sample pad where it characterized the sample. To make it suitable for the ideal detection after the sample pad, the sample is moved to another pad called a conjugate pad where several interactions take place then the sample is passed to the membrane which mainly consists of two lines that is, test line and control line. At last, the sample reached the absorbent pad where it offers sufficient bed volume to complete the sample flow. After the incubation step, the single line is visible on the pad which defines the +ve/-ve results of this test. A general diagrammatic representation of LFA is shown in Fig. 2.5 [60].

Likewise, this assay is also suitable and simple for the detection of COVID-19 by dropping the COVID patients' blood samples on the pad. Then buffer is used which makes the sample movable. Then the antibodies are bind to the chemicals which are against SARS-CoV-2. As the sample

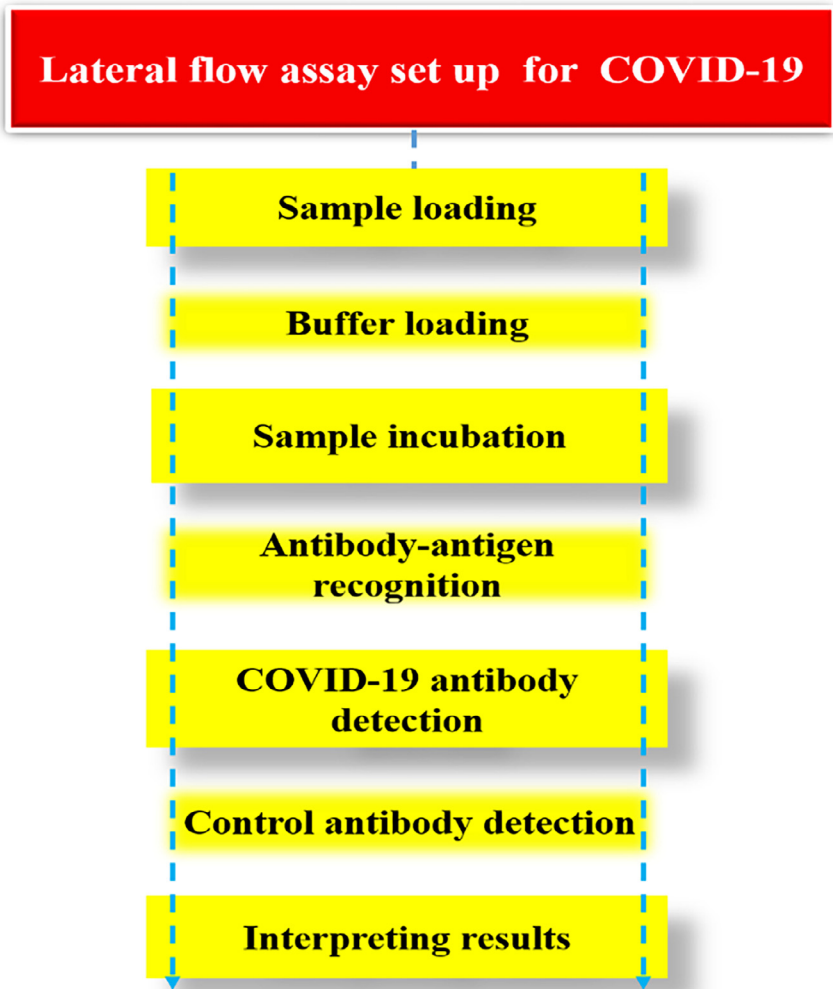


FIGURE 2.6 Flow chart of LFA to detect COVID-19.

moves through the device then the test and control lines (sometimes it may be three lines depending upon the antibodies) capture the antibodies and give color, which interprets the results of this device. The flow chart of LFA set up for the detection of COVID-19 is shown in Fig. 2.6 [61]. Again in 2020, LFA was employed by a group of scientists for detecting COVID-19 antibodies. About 11 LFA were compared and characterized for their performance in a population. Two cohorts were employed—350 blood donors from past influenza-affected ones and 110 samples from past negative PCR tested ones. Nine out of 11 showed a specificity of less than 88%,

while five of them showed sensitivity as same as ELISA. And only one of 11 fulfilled both of the situations. Therefore it was concluded from the study that this needs more negative cohorts and more positive diverse COVID-19 positive samples [62]. The first time a surface-enhanced Raman scattering-based LFA was utilized to diagnose COVID-19 by Liu H et al. As high-performance SERS tags, a new SiO₂@Ag nanocomposite labeled with dual layers of DTNB was used. With the SERS-LFIA, anti-SARS-CoV-2 IgM and IgG can be detected simultaneously and with high sensitivity. The SERS-LFIA was shown to be 100% accurate and precise in a study of 68 clinical serum samples [63]. Broughton JP et al. reported the rapid diagnosis of SARS-CoV-2 with the help of CRISPR (clustered regularly interspaced short palindromic repeats)-based DETECTR method followed by LFA assay. Sampling is done by extracting the RNA from the respiratory swab. The RT-PCR method is also used to compare the results from both methods. (SARS-CoV-2 DETECTR, RT-LAMP/Cas12 – LOD – 10 copies/μL input, CDC SARS-CoV-2 CoV-2 q RT-PCR–4.2 copies/μL input) [64].

2.5.4 Colorimetric assay

It is one of the simple and cheap methods of detection. Hence, it can make very easy on-site/real-time diagnosis [65]. Chow FW et al. are diagnosed SARS-CoV-2 with the help of a colorimetric assay that leads to color change, and then results can be seen via naked eyes, for this, it established a one-step colorimetric reverse-transcriptional loop-mediated isothermal amplification assay (COVID-19-LAMP) and detect SARS-CoV-2 with the LOD-42 copies per reaction [66]. Lalli MA et al. are demonstrated a rapid and RNA extraction-free detection of SARS CoV-2 in the human samples with the help of colorimetric RT-LAMP (reverse- transcription loop-mediated isothermal amplification) with the limit of detection- 59 particle copies per reaction. This research also highlights the flexibility of LAMP assay implementation using three outcomes- (a) Naked-eye colorimetric, (b) spectrometry, and (c) real-time fluorescence [67]. Garcia et al. introduced a versatile, colorimetric RT-lamp assay for the detection of SARS-CoV-2 RNA in samples by targeting gene N through a specific sequences primer set N15 (sequences are presented in Table 2.4). The results can be diagnosed as soon as 9 minutes after the reaction begin and obtain close to 100% sensitivity within 60 minutes with LOD of 200 copies of SARS-CoV-2 RNA/reaction and study was compared with RT-qPCR [68]. Nawattanapaiboon et al. developed a one-pot visual diagnosis platform to detect coronavirus SARS-CoV-2 with the help of colorimetric RT-LAMP with the LOD- 250 copies of SARS-CoV-2 RNA/reaction and this assay require only 1 hour throughout the practical along with 99.86% accuracy [69]. Gonzalez et al. are developed a colorimetric LAMP assay to detect SARS-CoV-2 nucleic acids in the range of $62-2 \times 10^5$ DNA copies. They utilize synthetic samples (with 100%

TABLE 2.4 Primer set for the detection for SARS CoV-2.

Set	Primer ¹	Sequence (5'→3')	Length (nt)	Gene position	Reference
N15 ⁴	F3	AGATCACATTGGCACCCG	18	28,703–28,915	[68]
	B3	CCATTGCCAGCCATTCTAGC	20		
	FIP	TGCTCCCTTCTGCGTAGAAGCCA- ATGCTGCAATCGTGCTAC	41		
	BIP	GGCGGCAGTCAAGCCTCTTCCCT- ACTGCTGCCTGGAGTT	39		
	LF	GCAATGTTGTTTCCTTGAGGAAGTT	24		
	LB	CCTCATCACGTAGTCGCAACAG	22		

accuracy) and RNA extracts from the COVID patients (sensitivity- 92.85%, specificity- 81.25%) [70]. Another author Moon et al. used this colorimetric assay to detect SARS-CoV-2 NI, N2, N3 genes, and drug-resistance pINI by utilizing CRISPER/dCAS-9 [70].

Various biosensors based on lab on a chip for the diagnosis of COVID-19 are summarized in Table 2.5, along with their strengths and limitations.

2.6 Conclusion and future aspects

Diagnosis is a big issue in today's world, particularly in heavily populated countries. If the COVID-19 disease has been identified, the disease's treatment and spread can be effectively managed. As a result, there is a crucial need to create a low-cost new technique, such as lab-on-chip biosensors, for a quick point of care diagnosis, so that patients can quickly quarantine/self-isolate, significantly reducing the risk of further infection. While neither traditional methods (qRT-PCR) nor lab-on-chip based biosensors is perfect instruments for COVID-19 diagnosis, these techniques should be used in tandem. Lab-on-chip biosensors, such as LFA, electrochemical, colorimetric approaches, on the other hand, are more compact, allowing for field use since they do not necessitate the use of laboratory equipment. Rather than nucleic acids, these systems seem to rely on detecting antibodies to and antigens upon the virus itself. On a small platform, these innovations demonstrate promise as a replacement for serology studies. On the other hand, plasmonic biosensors require a good laboratory setup but offer greater productivity, permitting the detection of several samples at the same time. The electrochemical and plasmonic assays have the quickest readout among all the lab-on-chip

TABLE 2.5 Various types of labs-on-chip based biosensor along with their strengths and limitations.

	Electrochemical biosensor,	Plasmonic biosensor	Lateral flow assay	Colorimetric assay
Strengths	<ul style="list-style-type: none"> – Electrochemical biosensors will deliver a more affordable price per analysis than RT-PCR. 	<ul style="list-style-type: none"> – Miniaturization, low cost, and user friendliness are all trends in SPR sensor interface design. It enables label-free, high-reliability, sensitivity, and real-time measurement. 	<ul style="list-style-type: none"> – Very low relative cost, can be done at the point of treatment or at home, is simple to use, and produces fast results. 	<ul style="list-style-type: none"> – Easy operation – Rapid detection. – Highly stable at room temperature.
Limitations	<ul style="list-style-type: none"> – The manufacturing of biosensors takes a longer time. – In case of multiple sequential reactions, the biosensor response time often increases. 	<ul style="list-style-type: none"> – Small analytes are not appropriate for examination with the SPR. Rather small analytes yield very small responses since the SPR measures the mass of the compounds that bind to the sensor surface. 	<ul style="list-style-type: none"> – Extensive monitoring of cross-reactivity with other immune responses is needed, as is variation in test specificity between manufacturers. – The technology is latest, and the evidence for its accuracy in diagnosing coronaviruses is still being assessed. 	<ul style="list-style-type: none"> – Requires careful cross-reactivity testing with other immune responses, as well as a laboratory setting. – Limited sensitivity

TABLE 2.6 Summary of LOC biosensor based on their principle/transducer for COVID-19 detection.

Lab-on-chip biosensors	Principle/transducer	Detection	Response time	Limit of detection	References
Electrochemical	Paper-based electrochemical sensor chip	SARS-CoV-2	5 minutes	6.9 copies/ μ L	[68]
	Isothermal rolling circle amplification (RCA)	SARS-COV-2 (N and S genes)	Less than 2 hours	1 copy/ μ L	[48]
	Cobalt-functionalized TiO ₂ nanotubes (Co-TNTs)	SARS-CoV-2 (spike -RBD)			[46]
	Electrochemical immunoassay	SARS-CoV-2 (Spike and nucleocapsid)	30 minutes	19 ng/mL for S and 8 ng/mL for N protein	[47]
	Ultrasensitive electrochemical	SARS-CoV-2 RNA	2 hours	200 copies/mL	[34]
	Optomicrofluidic chip based electrochemical biosensor	Antibody of SARS-CoV-2 spike protein		\sim 0.5 p.m	[49]
Plasmonic	A novel NIR plasmonic biosensor by combining promising 2D tellurene-MoS ₂ -COOH van der Waals heterostructure with plasmonic ITO film	SARS-CoV-2 and its S protein		Linear detection range of S and SARS-CoV-2 -s \sim 0–301.67 nM and \sim 0–67.8762 nM respectively.	[54]
	A dual-functional plasmonic biosensor combining the plasmonic photothermal (PPT) effect and localized surface plasmon resonance (LSPR) sensing transduction	SARS-CoV-2		0.22 pM	[55]
	SPR biosensor	Coronavirus 2 nucleoprotein		1.02 pM	[56]

(continued on next page)

LFA	Clinical characterization of Eleven LFA	SARS-CoV-2			[47]
	SERS-based LFA	Covid-19		LOD is 800 times higher than that of standard Au NPS-based LFIA for target IgM/IgG. And the LOD of SERS is 1 pg per mL	[63]
Colorimetric	CRISPER-cas12 based LFA	SARS-CoV-2	30 minutes	10 copies per μ L input	[64]
	A one step colorimetric reverse-transcriptional loop-mediated isothermal amplification assay	SARS-CoV-2 RNA		42 copies	[66]
	RT-LAMP	SARS-CoV-2		59 copies	[67]
	RT-LAMP	ORF1ab and N genes	60 minutes	200 copies of SARS-CoV-2 RNA/reaction	[68]
	RT-LAMP	RNA- dependent RNA polymerase gene (RdRp)	60 minutes	125 copies per reaction of SARS-CoV-2 RNA	[69]
	LAMP	N protein	50 minutes	$62 \cdot 2 \times 10^5$ DNA copies	[70]
	CRISPER/d cas-9	N1.n2.n3 genes	~2 hours	30 pM	[71]

biosensor technologies, however, the LFA and colorimetric biosensor takes time to develop a response perception diagnosis.

References

- [1] K. Yuki, M. Fujiogi, S. Koutsogiannaki, COVID-19 pathophysiology: A review, *Clin. Immunol.* 215 (2020) 108427.
- [2] S. Shafiee, S. Davaran, A mini-review on the current COVID-19 treatments, *Chemical Review and Letters* 3 (1) (2020 Jan 1) 19–22.
- [3] C.-C. Lai, T.-P. Shih, P.-R. Hsueh, H.-J. Tang, W.-C. Ko, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19): The epidemic and the challenges, *Int. J. Antimicrob. Agents* 55 (3) (2020) 105924.
- [4] F. Wu, H. Yi, Z. Su, S. Zhi-Gang, W. Wen, C. Yan-Mei, A new coronavirus associated with human respiratory disease in China, *Nature* 579 (7798) (2020) 265–269.
- [5] I. Glowacka, et al., Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response, *J. Virol.* 85 (9) (2011) 4122–4134.
- [6] P. V'kovski, A. Kratzel, S. Steiner, H. Stalder, V. Thiel, Coronavirus biology and replication: implications for SARS-CoV-2, *Nat. Rev. Microbiol.* 19 (3) (2021 Mar) 155–170.
- [7] M.A. Shereen, et al., COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses, *J. Adv. Res.* 24 (2020) 91–98.
- [8] S. Chen, J. Yang, W. Yang, C. Wang, T. Bärnighausen, COVID-19 control in China during mass population movements at New Year, *The Lancet* 395 (10226) (2020) 764–766.
- [9] C. Zhou, G. Chen, X. Yuanliang, X. Maosheng, et al., COVID-19 with spontaneous pneumomediastinum, *Lancet Infect. Dis.* 20 (4) (2020) 510.
- [10] S. Suleman, S.K. Shukla, N. Malhotra, S.D. Bukkitgar, N.P. Shetti, R. Pilloton, et al., Point of care detection of COVID-19: Advancement in biosensing and diagnostic methods, *Chem. Eng. J.* 414 (2021) 128759.
- [11] J.R. Choi, Development of point-of-care biosensors for COVID-19, *Frontiers in chemistry* 8 (2020) 517.
- [12] M.R. Hasan, P. Sharma, N. Anzar, C.S. Pundir, R. Pilloton, J. Narang, et al., Analytical methods for detection of human cytomegalovirus clinched biosensor a cutting-edge diagnostic tool, *Biomedical Engineering Advances* 1 (2021) 100006.
- [13] P.R. Coulet, What is a biosensor, *Biosensor Principles and Applications*, Boca Raton, 1991, pp. 1–6. (Book Reference).
- [14] N. Anzar, M.R. Hasan, M. Akram, N. Yadav, J. Narang, Systematic and validated techniques for the detection of ovarian cancer emphasizing the electro-analytical approach, *Process Biochem.* 94 (2020 Apr 13) 126–135.
- [15] M.A. Alam, M.R. Hasan, N. Anzar, S. Suleman, J. Narang, Diagnostic approaches for the rapid detection of Zika virus-A review, *Process Biochem.* 101 (2020 Nov 15) 156–168.
- [16] S. Patel, R. Nanda, S. Sahoo, E. Mohapatra, Biosensors in health care: the milestones achieved in their development towards lab-on-chip-analysis, *Biochem. Res. Int.* 2016 (2016 Mar 3) 1–12.
- [17] S. Gupta, K. Ramesh, S. Ahmed, V. Kakkar, Lab-on-chip technology: A review on design trends and future scope in biomedical applications, *Int. J. Biosci.* 8 (2016) 311–322.
- [18] A.T. Giannitsis, Microfabrication of biomedical lab-on-chip devices. A review, *Est. J. Eng.* 17 (2) (2011 Jun 1) 109.
- [19] C. Tymm, J. Zhou, A. Tadimety, A. Burklund, J.X. Zhang, Scalable COVID-19 detection enabled by lab-on-chip biosensors, *Cell. Mol. Bioeng.* 13 (4) (2020 Aug) 313–329.

- [20] Q. Hui, Y. Pan, Z. Yang, Paper based devices for rapid diagnostics and testing sewage for early warning of COVID-19 outbreak, *Case Studies in Chemical and Environmental Engineering* 2 (2020) 100064.
- [21] J.X. Zhang, K. Hoshino, *Molecular Sensors and Nanodevices: Principles, Designs and Applications in Biomedical Engineering*, Academic Press, United states, 2018 Nov 19.
- [22] L.Y. Wing, Z. ShiYun, C. Pang, M. Hazren, S.A. Kumar, W.C. Chung, Optimization studies of lift-off methods and its application in electrochemical biosensors, in: *In2014 IEEE 16th Electronics Packaging Technology Conference (EPTC)*, IEEE, 2014 Dec 3, pp. 768–773.
- [23] A. Gautam, C. Singhal, A. Mishra, A.T. John, U.K. Gautam, R. Abolhassani, R. Adelung, D. Kumar Avasthi, Y. Kumar Mishra, Detection of prostate cancer DNA using tetrapods based disposable paper ecofriendly biosensor device, *Medical Devices & Sensors* 3 (6) (2020 Dec) e10122.
- [24] M.R. Hasan, N. Anzar, M. Tyagi, N. Yadav, J. Narang, *Lab-on-a-chip devices—Advancement in the designing of biosensors, Functionalized Nanomaterials Based Devices for Environmental Applications*, Elsevier, Netherlands, 2021 Jan 1, pp. 175–198.
- [25] D.U. Xiaoguang, G. Yanxia, W. Furen, F. Zhaolun, Fabrication of poly (methyl methacrylate)(PMMA) microfluidic chips by a simple hot embossing method, *Chemical Journal of Chinese Universities* 24 (11) (2003 Jan 1) 1962–1966.
- [26] K.I. Kamei, Y. Mashimo, Y. Koyama, C. Fockenberg, M. Nakashima, M. Nakajima, J. Li, Y. Chen, 3D printing of soft lithography mold for rapid production of polydimethylsiloxane-based microfluidic devices for cell stimulation with concentration gradients, *Biomed. Microdevices* 17 (2) (2015 Apr) 1–8.
- [27] A. Yakoh, U. Pimpitak, S. Rengpipat, N. Hirankarn, O. Chailapakul, S. Chaiyo, based electrochemical biosensor for diagnosing COVID-19: Detection of SARS-CoV-2 antibodies and antigen, *Biosens. Bioelectron.* 176 (2021 Mar 15) 112912.
- [28] B. Giri, S. Pandey, R. Shrestha, K. Pokharel, F.S. Ligler, B.B. Neupane, Review of analytical performance of COVID-19 detection methods, *Analytical and bioanalytical chemistry* 413 (1) (2021 Jan) 35–48.
- [29] R.H. Sedlak, K.R. Jerome, Viral diagnostics in the era of digital polymerase chain reaction, *Diagn. Microbiol. Infect. Dis.* 75 (1) (2013 Jan 1) 1–4.
- [30] Tan C, Fan D, Wang N, Wang F, Wang B, Zhu L, Guo Y. Applications of digital PCR in COVID-19 pandemic. *View*.:20200082.
- [31] P. Poggio, P. Songia, C. Vavassori, V. Ricci, C. Banfi, S.S. Barbieri, G. Garoffolo, V.A. Myasoedova, L. Piacentini, A. Raucci, A. Scopece, Digital PCR for high sensitivity viral detection in false-negative SARS-CoV-2 patients, *Sci. Rep.* 11 (1) (2021 Feb 22) 1–7.
- [32] Y.I. Wong, S.Y. Lau, K.K. To, B.W. Mok, P. Wang, S. Deng, et al., Natural transmission of bat-like severe acute respiratory syndrome coronavirus 2 without proline-arginine-arginine-alanine variants in coronavirus disease 2019 patients, *Clin. Infect. Dis.* 73 (2020) 437–444.
- [33] V. Shah, R. Keniya, A. Shridharani, M. Punjabi, J. Shah, N. Mehendale, Diagnosis of COVID-19 using CT scan images and deep learning techniques, *Emerg. Radiol.* 28 (3) (2021) 1–9.
- [34] W. Zhao, Z. Zhong, X. Xie, Q. Yu, J. Liu, Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study, *Am. J. Roentgenol.* 214 (5) (2020 May) 1072–1077.
- [35] R. Nouri, Z. Tang, M. Dong, T. Liu, A. Kshirsagar, W. Guan, CRISPR-based detection of SARS-CoV-2: A review from sample to result, *Biosens. Bioelectron.* 178 (2021) 113012.
- [36] C. Lucia, P.B. Federico, G.C. Alejandra, An ultrasensitive, rapid, and portable coronavirus SARS-CoV-2 sequence detection method based on CRISPR-Cas12, *BioRxiv* (2020 Jan 1) 1–10.

- [37] S.D. Bukkittgar, N.P. Shetti, T.M. Aminabhavi, Electrochemical investigations for COVID-19 detection-A comparison with other viral detection methods, *Chem. Eng. J.* 420 (2020) 127575 Nov 2.
- [38] D.L. Lubell, Drawbacks and limitations of computed tomography, *Tex. Heart Inst. J.* 32 (2) (2005) 250.
- [39] A.A. Kojabad, M. Farzanehpour, H.E. Galeh, R. Dorostkar, A. Jafarpour, M. Bolandian, M.M. Nodooshan, Droplet digital PCR of viral DNA/RNA, Current progress, challenges, and future perspectives, *J. Med. Virol.* 93 (7) (2021 Feb 4) 4182–4197.
- [40] Liu H, dwita Lestari S. Application of digital PCR (dPCR) in the detection of Covid-19 in food. InE3S Web of Conferences 2021 May (Vol. 271, p. 02022). EDP Sciences.
- [41] N. Munawar, A. Ahmad, CRISPR/Cas System: An Introduction, CRISPR Crops, Springer, Singapore, 2021, pp. 1–35.
- [42] M.G. Dastidar, S. Roy, Public health management during COVID-19 and applications of point-of-care based biomolecular detection approaches, Environmental and Health Management of Novel Coronavirus Disease (COVID-19), Academic Press, United States, 2021 Jan 1, pp. 345–378.
- [43] J. Kudr, P. Michalek, L. Ilieva, V. Adam, O. Zitka, COVID-19: a challenge for electrochemical biosensors, *TrAC Trends Anal. Chem.* 136 (2021 Jan 18) 116192 116192.
- [44] M. Alafeef, K. Dighe, P. Moitra, D. Pan, Rapid, ultrasensitive, and quantitative detection of SARS-CoV-2 using antisense oligonucleotides directed electrochemical biosensor chip, *ACS nano* 14 (12) (2020 Oct 20) 17028–17045.
- [45] H. Zhao, F. Liu, W. Xie, T.C. Zhou, J. OuYang, L. Jin, H. Li, C.Y. Zhao, L. Zhang, J. Wei, Y.P. Zhang, Ultrasensitive supersandwich-type electrochemical sensor for SARS-CoV-2 from the infected COVID-19 patients using a smartphone, *Sens. Actuators B* 327 (2021 Jan) 128899.
- [46] B.S. Vadlamani, T. Uppal, S.C. Verma, M. Misra, Functionalized TiO₂ nanotube-based electrochemical biosensor for rapid detection of SARS-CoV-2, *Sensors* 20 (20) (2020 Jan) 5871.
- [47] L. Fabiani, M. Saroglia, G. Galatà, R. De Santis, S. Fillo, V. Luca, G. Faggioni, N. D'Amore, E. Regalbuto, P. Salvatori, G. Terova, Magnetic beads combined with carbon black-based screen-printed electrodes for COVID-19: A reliable and miniaturized electrochemical immunosensor for SARS-CoV-2 detection in saliva, *Biosens. Bioelectron.* 171 (2021) 112686.
- [48] T. Chaibun, J. Puenpa, T. Ngamdee, N. Boonapatcharoen, P. Athamanolap, A.P. O'Mullane, S. Vongpunsawad, Y. Poovorawan, S.Y. Lee, B. Lertanantawong, Rapid electrochemical detection of coronavirus SARS-CoV-2, *Nat. Commun.* 12 (1) (2021 Feb 5) 1–10.
- [49] R. Funari, K.Y. Chu, A.Q. Shen, Detection of antibodies against SARS-CoV-2 spike protein by gold nanospikes in an opto-microfluidic chip, *Biosens. Bioelectron.* 169 (2020 Dec 1) 112578.
- [50] J.R. Mejía-Salazar, O.N. Oliveira Jr, Plasmonic biosensing: focus review, *Chem. Rev.* 118 (20) (2018 Sep 24) 10617–10625.
- [51] M. Asif, M. Ajmal, G. Ashraf, N. Muhammad, A. Aziz, T. Iftikhar, J. Wang, H. Liu, The role of biosensors in COVID-19 outbreak, *Current Opinion in Electrochemistry* 23 (2020 Sep 18) 174–184.
- [52] A. Djaileb, B. Charron, M.H. Jodaylami, V. Thibault, J. Coutu, K. Stevenson, S. Forest, L.S. Live, D. Boudreau, J.N. Pelletier, J.F. Masson, A rapid and quantitative serum test for SARS-CoV-2 antibodies with portable surface plasmon resonance sensing, *ChemRxiv* 15 (2020 Apr 15) 10–26434 April.
- [53] R. Samson, G.R. Navale, M.S. Dharne, Biosensors: frontiers in rapid detection of COVID-19, *3 Biotech* 10 (9) (2020 Sep) 1–9.

- [54] X. Peng, Y. Zhou, K. Nie, F. Zhou, Y. Yuan, J. Song, J. Qu, Promising near-infrared plasmonic biosensor employed for specific detection of SARS-CoV-2 and its spike glycoprotein, *New J. Phys.* 22 (10) (2020 Oct 21) 103046.
- [55] G. Qiu, Z. Gai, Y. Tao, J. Schmitt, G.A. Kullak-Ublick, J. Wang, Dual-functional plasmonic photothermal biosensors for highly accurate severe acute respiratory syndrome coronavirus 2 detection, *ACS nano* 14 (5) (2020 Apr 13) 5268–5277.
- [56] J.H. Bong, T.H. Kim, J. Jung, S.J. Lee, J.S. Sung, C.K. Lee, M.J. Kang, H.O. Kim, J.C. Pyun, Pig Sera-derived Anti-SARS-CoV-2 Antibodies in Surface Plasmon Resonance Biosensors, *Biochip Journal* 14 (4) (2020 Dec) 358–368.
- [57] D.D. Liana, B. Raguse, J.J. Gooding, E. Chow, Recent advances in paper-based sensors, *sensors* 12 (9) (2012 Sep) 11505–11526.
- [58] M. Pohanka, Point-of-Care Diagnoses and Assays Based on Lateral Flow Test, *Int. J. Environ. Anal. Chem.* 2021 (2021 Jan 20) 1–9.
- [59] T. Mahmoudi, M. de la Guardia, B. Baradaran, Lateral flow assays towards point-of-care cancer detection: A review of current progress and future trends, *TrAC Trends Anal. Chem.* 125 (2020 Apr 1) 115842.
- [60] C. Parolo, A. Sena-Torralba, J.F. Bergua, E. Calucho, C. Fuentes-Chust, L. Hu, L. Rivas, R. Álvarez-Diduk, E.P. Nguyen, S. Cinti, D. Quesada-González, Tutorial: design and fabrication of nanoparticle-based lateral-flow immunoassays, *Nat. Protoc.* 15 (12) (2020 Dec) 3788–3816.
- [61] K. Green, A. Winter, R. Dickinson, S. Graziadio, R. Wolff, S. Mallett, A.J. Allen, What tests could potentially be used for the screening, diagnosis and monitoring of COVID-19 and what are their advantages and disadvantages, *CEBM2020* 13 (2020 Apr).
- [62] F. Rudolf, H.M. Kaltenbach, J. Linnik, M.T. Ruf, C. Niederhauser, B. Nickel, D. Gygax, M. Savic, Clinical characterisation of eleven lateral flow assays for detection of COVID-19 antibodies in a population, *MedRxiv* (2020 Jan 1).
- [63] H. Liu, E. Dai, R. Xiao, Z. Zhou, M. Zhang, Z. Bai, Y. Shao, K. Qi, J. Tu, C. Wang, S. Wang, Development of a SERS-based lateral flow immunoassay for rapid and ultra-sensitive detection of anti-SARS-CoV-2 IgM/IgG in clinical samples, *Sens. Actuators B* 329 (2021 Feb 15) 129196.
- [64] Broughton JP, Deng X, Yu G, Fasching CL, Singh J, Streithorst J, Granados A, Sotomayor-Gonzalez A, Zorn K, Gopez A, Hsu E. Rapid Detection of 2019 Novel Coronavirus SARS-CoV-2 Using a CRISPR-based DETECTR Lateral Flow Assay. 2020 Mar; 10: 1–27.
- [65] J. Liu, Y. Lu, A colorimetric lead biosensor using DNAzyme-directed assembly of gold nanoparticles, *J. Am. Chem. Soc.* 125 (22) (2003 Jun 4) 6642–6643.
- [66] F.W. Chow, T.T. Chan, A.R. Tam, S. Zhao, W. Yao, J. Fung, F.K. Cheng, G.C. Lo, S. Chu, K.L. Aw-Yong, J.Y. Tang, A rapid, simple, inexpensive, and mobile colorimetric assay COVID-19-LAMP for mass on-site screening of COVID-19, *Int. J. Mol. Sci.* 21 (15) (2020 Jan) 5380.
- [67] M.A. Lalli, J.S. Langmade, X. Chen, C.C. Fronick, C.S. Sawyer, L.C. Burcea, M.N. Wilkinson, R.S. Fulton, M. Heinz, W.J. Buchser, R.D. Head, Rapid and extraction-free detection of SARS-CoV-2 from saliva by colorimetric reverse-transcription loop-mediated isothermal amplification, *Clin. Chem.* 67 (2) (2021 Feb) 415–424.
- [68] J. García-Bernalt Diego, P. Fernández-Soto, M. Domínguez-Gil, M. Belhassen-García, J.L. Bellido, A. Muro, A Simple, Affordable, Rapid, Stabilized, Colorimetric, Versatile RT-LAMP Assay to Detect SARS-CoV-2, *Diagnostics* 11 (3) (2021 Mar) 438.
- [69] K. Nawattanapaiboon, E. Pasomsab, P. Prombun, A. Wongbunmak, A. Jenjitwanich, P. Mahasupachai, P. Vetcho, C. Chayrach, N. Manatjaroenlap, C. Samphaongern, T. Watthanachockchai, Colorimetric reverse transcription loop-mediated isothermal amplification (RT-LAMP) as a visual diagnostic platform for the detection of the emerging coronavirus SARS-CoV-2, *Analyst* 146 (2) (2021) 471–477.

- [70] E. González-González, I.M. Lara-Mayorga, I.P. Rodríguez-Sánchez, Y.S. Zhang, S.O. Martínez-Chapa, G. Trujillo-de Santiago, M.M. Alvarez, Colorimetric loop-mediated isothermal amplification (LAMP) for cost-effective and quantitative detection of SARS-CoV-2: the change in color in LAMP-based assays quantitatively correlates with viral copy number, *Anal. Methods* 13 (2) (2021) 169–178.
- [71] J. Moon, H.J. Kwon, D. Yong, I.C. Lee, H. Kim, H. Kang, E.K. Lim, K.S. Lee, J. Jung, H.G. Park, T. Kang, Colorimetric detection of sars-cov-2 and drug-resistant ph1n1 using crispr/dcas9, *ACS sensors* 5 (12) (2020 Dec 3) 4017–4026.
- [72] J. Kudr, P. Michalek, L. Ilieva, V. Adam, O. Zitka, COVID-19: a challenge for electrochemical biosensors, *TrAC Trends Anal. Chem.* (2021 Jan 18) 116192.
- [73] I.S. Kucherenko, O.O. Soldatkin, S.V. Dzyadevych, A.P. Soldatkin, Electrochemical biosensors based on multienzyme systems: Main groups, advantages and limitations—A review, *Anal. Chim. Acta* 1111 (2020 May 15) 114–131.
- [74] S.A. Abid, A. Suhail, I.M. Al-Kadmy, A.A. Sattar, A.M. Beshbishy, G.E. Batiha, et al., Biosensors as a future diagnostic approach for COVID-19, *Life Sci.* 273 (Jan 26) (2021) 119117.
- [75] K. Green, A. Winter, R. Dickinson, S. Graziadio, R. Wolff, S. Mallett, A.J. Allen, What tests could potentially be used for the screening, diagnosis and monitoring of COVID-19 and what are their advantages and disadvantages, *CEBM2020* 13 (2020 Apr).
- [76] F. Charbgo, M. Ramezani, M. Darroudi, Bio-sensing applications of cerium oxide nanoparticles: advantages and disadvantages, *Biosens. Bioelectron.* 96 (2017 Oct 15) 33–43.

Non-Print Items

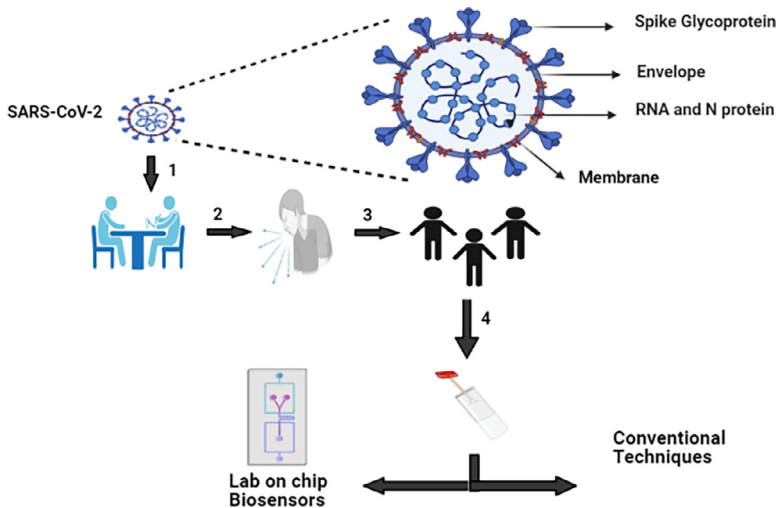
Abstract

In December 2019, a disease linked to the coronavirus (CoV) was identified in the capital of China's Wuhan. When seen under an electron microscope, CoVs, which are enveloped positive-sense RNA viruses, appear like crown-shaped viruses. There are four subtypes of CoVs such as (a) alpha, (b) beta, (c) delta, (d) gamma CoV. Coronavirus disease is caused by the extreme acute respiratory syndrome coronavirus 2, which is caused by a beta coronavirus (-CoVs or Beta-CoVs) (SARS-CoV-2). Infected people may have fever of 38°C, cough, and shortness of breath. WHO officially called COVID-19, an abbreviated form of coronavirus disease 2019, on February 12, 2020.

Keywords

COVID-19; SARS-CoV-2; Biosensor; Coronavirus; RT-PCR

Graphical abstract



Highlights

- The initial transmission of SARS-CoV2 from animals to humans
- Transmission and spread of disease from one human to another
- Infected droplets released through coughing and sneezing from patient and community transfer among individuals through infected droplets
- Collection of sample and detection of SARS-CoV2 with the help of conventional methods and lab-on-chip biosensor.