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Innovative and Rapid Detection Methods for SARS-CoV-2 Infections: Recent Developments Worldwide

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Authors' contributions

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ABSTRACT

There are no effective treatments for COVID-19 caused by SARS-CoV-2 viruses worldwide and the effects of vaccines on new genetic variants of the virus are still uncertain. Therefore, initial diagnosis and management are essential for controlling the pandemic. The conventional diagnosis methods for SARS-CoV-2 include molecular tests, serology tests, and computed tomography (CT). However, a few innovative, rapid, and promising detection methods were developed in the last year and this year in different countries of the world. We have discussed the advantages and challenges of these new diagnostic methods besides discussing the widely adopted conventional approaches mentioned above.

We have summarized the most recent and conventional diagnosis methods, including commercially available devices and kits according to their SARS-CoV-2 detection accuracy rates and completion times. We have also discussed the ongoing research in this field. Finally, we have identified some thrust areas of research that could help to identify the new variants of SARS-CoV-2 rapidly and accurately.

Our review findings indicate that CRISPR-based FELUDA, SHERLOCK, Hyris kit, and COVIRAP are low time consuming, user friendly, and very appropriate for low-resource countries. Although several diagnostic methods are available, we need more efficient diagnostic tools for SARS-CoV-2 with respect to cost efficiency, accuracy, rapid detection, and user-friendliness, especially for new variants in remote areas of the world.

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1. INTRODUCTION

On March 11, 2020, COVID-19 was announced as a worldwide pandemic by The World Health Organization. The World is still suffering from its hardship. In 2021, it spread out as a second wave with some mutated strains in different countries. The situation is worse now, especially in India, U.S.A., and Brazil. As per the report published by WHO on the date of July 19, the total number of authenticated cases of COVID-19 is 561,156,416. whereas the number of deaths is 6,365,510 worldwide. According to the same WHO report, a total of 12,166,921,655 vaccine doses have been administered [1]. There are many SARS-CoV-2 variants like alpha, beta, gamma, delta, which are highly transmissible. Now the dangerous and most transmissible delta variant is spreading throughout the World. It already spread out to nearly 100 countries, and in India, a mutated version of the delta variant of SARS-CoV-2, which is delta plus, is probably the most transmissible one [2]. As there is no specific drug for this disease and the vaccines available have limited accuracy on emerging strains, early diagnosis and management are vital to control the pandemic. And an essential feature is that it can be transmitted without the awareness of the host about the infection. Epidemiologic proof has indicated that pre-symptomatic and asymptomatic communication of the virus can drive the current epidemic. Identifying variants in a particular country and tracing their origin has become a top priority in the battle to control the COVID-19 pandemic. There are few primary approaches to SARS-CoV-2 detection - direct analysis of the virus by the spotting of nucleic acids or spotting via amplification of nucleic acids, and another one is serological or immunological tests to analyse the effects of infection by the virus in the host. Another one that is Rapid diagnostic test (RDT) of a sample of the respiratory tract of a person helps to determine the viral proteins (antigens) related to COVID-19 virus. Many molecular trials and immunoassays were quickly developed, though numerous are still waiting for regulatory approvals. Clinical validation and formal authorization are still waiting for some. It is reported that many symptomatic patients are negative after the PCR test, and the lesions identified the presence of viruses after the computed tomography (CT scan) report. Therefore, a CT scan was also recommended as the third required approach for confirming the SARS-CoV-2 diagnosis. The minimum sensitivity of the RT-PCR test is 95% [3], which means up to 5% false-negative results are expected. In the past few months, the COVID-19 virus has had a significant impact on clinical microbiology laboratories. Among the patient samples, sensitive and particular viral nucleic acid detection is crucial for clinical diagnostics, genotyping, and biotechnological advancements. However, there are many methods that are not up to the mark in the criteria of the sensitivity or the specificity to detect nucleic acids at low concentrations and are too costly, time-consuming, and complex to use outside of standard laboratory settings. In the case of the COVID-19 pandemic, RT-PCR can be used to diagnose the presence of SARS-CoV-2 RNA, but inadequate access to reagents and equipment has become a stumbling block. So, we need a more specific, accurate, user-friendly, rapid, and inexpensive SARS-CoV-2 test. We, therefore, have evaluated the performance of several diagnostics technology and their potential use in recent COVID-19 diagnoses, considering the quality-price and faster turnaround of results. Besides, we also thought about future tests, which are not only applicable for the SARS-CoV-2 virus but also for the detection of other secondary pathogens. We have discussed some promising tests, such as CRISPR Cas-based testing, aptamer-based testing, next-generation sequencing, etc., and other methods which are still in trial.

2. METHODS

This study is a non-systematic descriptive mini-review of the detection methods of SARS-CoV-2 viruses and detection of antibodies to SARS-CoV-2 virus, which were recently reported in scientific peer reviewed literature and in various news magazines and other online resources including editorials and blogs. Most of the methods were approved by FDA and different regulatory agencies worldwide. Some new methods which are still at trial mode were also considered. We have also reviewed clinical methods of COVID-19 diagnostics, such as X-ray and CT and other recently used innovative methods by clinicians worldwide. When comparing these methods, we have considered their costs, sensitivity, execution time, and compared them with the gold-standard

commercial diagnostic methods such as RT-PCR. Our thinking on the review of the possible new SARS-CoV-2 detection methods was initially informed by reflection on a series of discussions between authors. We further developed this thinking and refined the well-known methods available from various sources including National Library of Medicine's PubMed database, which comprises more than 34 million citations for biomedical literature from MEDLINE, life science journals, and online books. We have also considered articles and reports available in Google Scholar, which is a freely accessible web search engine that indexes the full text or metadata of scholarly literature across an array of publishing formats and disciplines. In addition, we have reviewed the news reports and blogs available online. All these three sources of data were utilized and summarized in this minireview.

2.1 Reverse Transcription-Loop-Mediated Isothermal Amplification (RT-LAMP)

A new diagnostic method called RT-LAMP, which is a one-step nucleic acid amplification method to multiply particular sequences of RNA of SARS-CoV-2 was evolved by a German research team and it is appropriate for other RNA viruses as well. Amplification at a constant the temperature, exclusion of a thermal cycler, a faster test result, and potentially a larger diagnostic capacity is some of the fundamental advantages possessed by this method. The RT-PCR test needs different temperatures in one cycle. The temperature of the solution has to be interchanged from 92°C to 56°C and again to 72°C in every two minutes. So, this test needs an expensive thermal cycle [4]. This process is equivalent to conventional PCR tests, with the deviation that nucleic acid amplification that take place at one temperature (65°C only). So, an expensive thermal cycle is not needed. The main advantages of this method are as follows: a. the assay is so fast that results can be obtained within 30 minutes, b. positive samples are amplified as early as within 10 minutes and c. it works in a wide pH range [5-6]. The cost of the LAMP diagnostic method is reasonable and does not need a complex. and expensive piece of equipment. The assays can be done with fewer skills and minimum infrastructure. It is an accurate, confirmatory, cost-effective, rapid, and user-friendly molecular diagnostic method which is the basic address to address a pandemic like COVID-19. For RT-PCR, isolation of RNA and specification of viral RNA are critical initial steps. The following steps involve the conversion of RNA to DNA and then a semi-quantitative reaction occurs using oligonucleotides specific for viral cDNA [7-11]. Most of the reagents in these processes are highly temperature-sensitive. In the case of RT-LAMP, this is a simplified version of the RT-PCR method. This method does not require an initial RNA isolation step [12-13]. So, another plus point of RT-LAMP is that the reagents can be stored at 4°C (ordinary household refrigerator). In contrast, the reagents for RT-PCR require storage and transport at -20°C, which escalates the cost.

There is an acute need for a user-friendly technique for COVID-19 testing in remote areas especially in highly populated countries like India. The RT-LAMP technique has been recently adopted in India with new trade names. Although the LAMP technique is familiar in Western countries for the past five years or more, the procedure is totally unique to the Indian in vitro diagnostic (IVD) market. The LAMP technology has been indigenously developed by Agape Diagnostics in India and ICMR (Indian Council of Medical Research) has approved and validated their kit which is named LUME ScreennCov [14]. The target genes of this system for SARS-CoV-2 are the N gene and RdRp gene and turnaround time is 10 to 35 minutes after RNA extraction with 98.7% sensitivity. And specificity compared with RT-PCR is 100%.

The negative aspect of the LAMP is specificity to COVID-19 only. It can inform whether a person is infected or not with SARS-CoV-2 or other RNA viruses but cannot give information on other diseases or symptoms that have been secondarily developed after COVID-19. This test is unable to inform clinicians if a patient has been previously infected with the virus or if a patient has developed any immunity against the virus.

2.2 Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) Based Testing

Recently the development of CRISPR-based methods has reshaped molecular diagnosis. It applies the cutting-edge CRISPR-Cas9 technology and Drs. Emmanuelle Charpentier and Jennifer A. Doudna bagged the Nobel Prize in Chemistry in 2020 for this. CRISPR-Cas9 is used by geneticists and medical researchers to manipulate parts of the genome by removing, adding, or altering sections of the DNA sequence. The advantages of the CRISPR system include specificity, speed, precision,

solidity, proficiency, and adaptability, which have motivated researchers to evolve RISPR-based diagnostic and therapeutic methods [15,16]. There are many types of new diagnostic methods designed based on CRISPR Cas technology, e.g., CRISPR Cas 12, CRISPR Cas 9, CRISPR Cas 19, etc.

Recently in the U.S.A. COVID-19 infections were detected among patients using CRISPR-Cas 12 based assay from extracted patient sample RNA which is known as SARS-CoV-2 DNA Endonuclease-Targeted CRISPR Trans reporter (DETECTOR) [16-18]. The reporting time of DETECTOR method is faster than PCR methods, and this was an excellent alternative diagnostic tool. Another CRISPER-based method is RNA-guided Cas13, which can identify the genomic characteristics of SARS-CoV-2 and provides an important detection strategy for SARS-CoV-2 [19-20] was developed by scientists from the Broad Institute of U.S. This method is named as SHERLOCK (specific high-sensitivity enzymatic reporter unlocking) test, which uses Cas12 for detection of SARS-CoV-2. SHERLOCK was first developed in 2017 and has been improved since then, and is currently being used in COVID-19 detections [21-23]. Both DETECTR and SHERLOCK utilize the promiscuous cleavage and degradation of neighbouring ssRNA and ssDNA by Cas 12a and Cas13, respectively, to cleave and activate a reporter. The signal from this reporter is easily detectable and can be quantified further to determine the presence and quantity of DNA, RNA or a mutation of interest in viral genome. Together these two methods demonstrated the excellent power of CRISPR-based diagnostic approach.

A unique diagnostic testing kit for COVID-19 was developed by Tata Medical and Diagnostics Ltd. (Tata MD) in India and disclosed as TATA MD CHECK, industrially. Tata MD CHECK is the FNCAS9 Editor-Limited uniform Detection Assay (FELUDA) method which is a CRISPR Cas 9-ased innovation that was introduced in India by the CSIR-Institute of Genomics and Integrative Biology (IGIB) for verifying COVID [24-26]. They have designed a guide RNA (a short synthetic RNA composed of a scaffold sequence necessary for Cas binding and a user-defined nucleotide spacer that defines the genomic target to be modified) complementary to target the SARS-CoV-2 genome sequence. The Tata CRISPR test is the world's first CRISPR Cas-9-based diagnostics method. In 'FELUDA', it works like a pregnancy detection strip and it changes colour if the virus is detected, and it is very user-friendly [27]. Feluda is the World's first COVID-19 detection test kit that uses Cas9. It was tested on 2000 patients and reported 96% sensitivity and 98% specificity and the results also supported by RT-PCR (comment of Harsh Vardhan, Union Health Minister of India).

2.3 The Hyris System™ COVID-19 Diagnostic Kit Developed in ITALY

The Hyris System™ is a detection tool for SARS-CoV-2, it works based on nucleic acid in nasopharyngeal swabs or nasal swabs specimens and was a miniature detected real-time PCR for the in vitro detection. This diagnostic kit is unique because it is very user-friendly and offers rapid diagnosis in any typical environmental setting, at any time. This kit were also utilizes the Artificial Intelligence, which provides real time access to results, already automatically interpreted, on its cloud-based software platform. Hyris Ltd. is a multinational Italian company that developed this diagnostic kit as a point-of-care rapid test "bKIT virus Finder COVID-19" [28-29]. The Hyris System™ identifies COVID-19 in samples collected from contaminated surfaces, which represent a potential threat for both patients and healthcare workers. The entire diagnosis time takes about an hour, which is another advantage. The procedures are simple as follows. The nasopharyngeal swabs are inserted into the nasal cavity and placed in vials, then 15 ml of reaction is added to the swab in the vial. These reagents present in the kit are designed to reduce the impact of the RNase contained in the clinical specimen which promotes nucleic acid extraction before the retro transcriptase step. Detection can be made through "positive" or "negative" results assigned by the samples. It is designed detected fluently and quickly to use in emergency conditions and remote areas. Hyris System™ provides more or less same results as RT-PCR method. It is a complete portable suite, which is versatile, fast, and reliable [30,31]. The main advantage of this test is it is fully automatic. In Canada, Hyris kit was recently approved as a point-of-care test. for human diagnostics. So, this test is very important for quick and prompt detection, and it can be used during traveling.

There have some negative aspects too when a patient with a viral load that is very close to the limit of detection of the method shows "false

negative" results. In some cases, it gives "inconclusive" results.

2.4 A New Low-Cost COVID-19 Diagnostic Test Developed in India, by IIT Kharagpur: COVIRAP

A new coronavirus diagnostic machine and test kit were recently developed by the researchers at the Indian Institute of Technology (IIT), Kharagpur, India, and was approved by the Indian Council of Medical Research (ICMR). The machine costs below $100 and one test costs approximately $8 to $10 only. During the testing conducted using 200 patient samples, the machine displayed over 93% sensitivity and almost 98% specificity. This highly promising and cheap diagnostic method showed an accuracy level slightly lower than RT-PCR method at a fraction of the cost. A Group of Companies, India, and Bramerton Holdings LLC, USA have been licensed for commercialization for this kit. The manufacturing cost is very low compared to a RT-PCR machine [32,33]. A generic step-wise isothermal nucleic acid-based testing technology used for the quick diagnosis of the pathogen. After getting the nasal swab or saliva samples the results could be available within 45 minutes only. Once the sample was processed in the machine after being mixed with solutions, treated paper strips-similar to pregnancy strips-are dipped into it, and the emergence of coloured lines will depict the presence of the virus, according to Kharagpur IIT team [34]. It is self-sufficient, does not depend on separate RNA extraction, is very affordable pre-programmable portable device. A free smartphone's app has also been developed to provide a simple interpretation of results to patients. A more advanced version of COVIRAP has also been developed using a step-wise isothermal nucleic acid testing technology for the rapid diagnosis of pathogenic infections including COVID-19 [35]. The COVIRAP platform is capable to diagnose other disease detections where pathogens are detectable by nucleic acid-based tests. This is not only for one-time diagnostic tests for COVID-19 but it will distinctive for global infectious disease diagnosis in the future. As stated above, COVIRAP requires small portable equipment, and ideal for use in rural areas and in less developed countries where air-conditioned laboratories are unavailable. The portable unit is very easy to operate with a minimum of training in all kind of environments [36,37]. Despite all these advantages, the negative aspect of COVIRAP is slightly lower sensitivity and specificity than RT-PCR [38].

2.5 Aptamer-based Testing

An aptamer is a single-stranded artificial nucleic acid that is used to detect pathogens. DNA aptamers have capability to bind with single-stranded DNA molecules to a particular target with high affinity and specificity. The aptamers were considered for COVID-19 diagnosis because of easy modification options and their high stability [39]. The aptamer-based strategy was recently considered as an up-and-coming method for the detection of the COVID-19. This method is an economical, accurate, and low-time-consuming test. Similar to antibodies, aptamers bind specifically to their targets. Aptamer targets include a variety of small molecules such as amino acids, nucleotides, and antibodies [40], but can also be larger, including proteins [41], viruses, and bacteria [42]. Aptamers can concede viral proteins and have been introduced in the rapid detection of viruses and also as antiviral agents in treating infection. The aptamer-based sensor works based on binding two aptamer probes to the same protein target that brings the ligation DNA region into close proximity, thereby initiating ligation-dependent qPCR amplification. By using a simple, equivalent, and fast detection workflow of 120 minutes this system discovers serum nucleocapsid protein [43].

During the outbreak of SARS-CoV in 2003, scientists reported that the nucleocapsid (N) protein of SARS-CoV-2 is an excellent diagnostic biomarker [44]. In the primary stage of coronavirus infection (day 1-10), the viral N protein is much more delicate for detection (90% positive) compared to viral nucleic acid (42.9%) or antibodies (21.4%) in patient's sera [45]. Thus, aptamer-based methods should be very effective for virus detection in the pioneer stages of SARS-CoV-2 infections. A research team from India, the Vellore Institute of Technology (VIT), has recently developed an aptamer-based point-of-care (POC) diagnostic kit for the quick diagnosis of COVID-19. Another research team from India, the translational Health Science and Technology Institute (THSTI) in Faridabad, has evolved an aptamer-linked immobilized sorbent assay (ALISA) for detecting SARS-Co-V2 [46,47]. For this test, the aptamer attaches to the full-length spike protein of the virus, which plays a vital role in binding to the receptors found on human cells, and gains entry into the cell. The

ALISA assay has 90% sensitivity and 99% specificity, according to the research team. The main advantage of this method is that it works on mutated strains also and has very little chance of false positive or negative resultants [48,49]. Some weakness of this testing method includes the release of aptamers through the renal system due to their low molecular weight. Another limitation is that the toxicity of aptamers on the human body is unknown at this time [50,51].

2.6 Next-Generation Sequencing (NGS)

Next-generation sequencing (NGS) is an enormous aligned sequencing technology, which can offer ultra-high throughput, expandability, and speed. This method can allow clinicians to test many genes of an infectious microorganism simultaneously. The NGS provides an effective way to identify the new coronavirus strains and their mutations, it's accustomed to determining the order of nucleotides in entire genomes or targeted regions of DNA or RNA. The NGS method can be effective with transmission tracing, rapid viral diagnosis, verifying the accuracy of other diagnostic tests, and checking antiviral vaccine effectiveness. By the use of next-generation sequencing, it can generate information about the genomic sequence of the virus which is present in a sample. The sequence data can be used not only for diagnosis but also for research purposes. The NGS method allows DNAs to be read directly, nucleotide by nucleotide, and is thus very effective for the diagnosis of mutated strains with altered genomes. So, in the long run, the NGS can help researchers and clinicians for adopting the proper identification and look into treatment options [52,53,54]. This method has 94% sensitivity and 100% specificity compared with the RT-PCR method.

The uses of NGS methods are of various types; among them, the shotgun method and the target enrichment method are fundamental to diagnosing SARS-CoV-2. A next-generation shotgun metagenomics method was developed by Illumina, which has the ability to detect not only coronavirus but also other pathogens which are present in the sample [55]. So, it will help patients get information about their disease very quickly in one test. Also, the NGS can be used to monitor the presence of harmful bacteria and viruses in environmental samples collected from surfaces and air. It provides high coverage uniformity, low duplication rates, and strand specificity with a streamline [56,57]. Understanding genomic mutations across different samples by the NGS can help understand the epidemiology of disease transmission [58]. With time, the NGS method is becoming cheaper, more accessible, faster, and more reliable. It is now becoming one of the gold-standard methods for clinical diagnosis [59].

2.7 Computed Tomography (CT) Scanning for Early Detection of SARS-CoV-2

In recent days, CT-Scan has been a very useful method that may be used for early COVID detection. Chest CT is a very important tool for pneumonia diagnosis, so it rapidly diagnoses COVID-related pneumonia also. The chest imagination related to COVID-19 was first published in January 2020 and included bilateral lung involvement and ground-glass opacities in the majority of hospitalized patients [60]. Chest CT is important to detect both alternative diagnoses and complications of COVID-19-related acute respiratory distress syndrome, pulmonary embolism, and heart failure, while its role in prognostication requires investigation. In an experiment, out of 240 patients, 60% had positive RT-PCR results, and 89% had positive chest CT scans. So, its sensitivity is higher than the RT-PCR test [61]. It should be used for those patients who may have classic symptoms of the illness but have a negative RT-PCR test result. CT scanning provides us with a powerful non-invasive means for the diagnosis and monitoring of COVID-19 [62,63]. This method is also applicable for situations when a CT pulmonary angiogram might be required to rule out pulmonary embolism in a patient who is on anticoagulants and steroids and is not showing any signs of recovery. This is also useful in cases where the patient is in intensive care units (ICUs). The usage of CT-Scan also diagnoses the dangerous COVID-19 associated fungal super-infectious like Aspergillosis or mucormycotic [64-66]. A consensus about the role of chest imaging (mainly CT scanning) in managing patients during the COVID-19 pandemic recently, the Fleischner society has published and discussed different clinical scenarios, including the seriousness of the respiratory disease, pre-test probability, risk factors for disease progression, and critical resource limitation [58]. High-risk hospitalized patients with co-morbidities, which may need advanced health care support, urgently need

chest CT scans. For the investigation of post-COVID infection complications and patients' pulmonary position, it is very important. The meta-analysis study showed that chest CT scans might be beneficial in the early detection of cases of COVID-19. According to the experimental reports, sensitivity and specificity values for CT scans were respectively 86.7% and 93.6%, in a recent meta-analysis including 63 studies [67,68].

The negative aspect of this test is that it does not properly distinguish between CoVID-19 and other respiratory infections, like bacterial pneumonia and seasonal flu. Another problem is that some patients with COVID-19 may have normal chest CT reports.

The table below shows the sensitivity and completion times of different new and classic diagnostic methods for COVID-19, adopted worldwide.

Table 1. Technologies based on accuracy levels

Technology	Sensitivity
RT-LAMP	97.5%
CRISPR Cas13 based SHERLOCK	97%
CRISPR Cas9based FELUDA	96%
Hyris Kit	95%
COVIRAP	94%
Aptamer based	90%
Next-generation sequencing	94%
CT scan	86.7%

Table 2. Technologies based on the completion times

Technology	Time requirement
RT-LAMP	30 minutes
FELUDA (CRISPR Cas9 based)	45 minute
CRISPR Cas13 based SHERLOCK	60 minute
CT Scan	60 minute
COVIRAP	60 minute
Hyris Kit	120 minute
Aptamer based	120 minute
Next generation sequencing	720 minute

Table 3. Technologies based on the cost

Technology	Cost
RT-LAMP	$37.79
FELUDA (CRISPR Cas9 based)	$6.29
CRISPR Cas13 based SHERLOCK	$50
CT Scan	$22.68
COVIRAP	$6.29
Hyris Kit	Not Known
Aptamer based	Not Known
Next generation sequencing	$15

3. OTHER RECENT DEVELOPMENTS

Finally, we will briefly discuss the most recent developments in the COVID-19 diagnostics in the last several months. Recently a novel sensor system was evolved that can detect SARS-CoV-2 from saliva samples in one second, which is much faster than the existing methods. In the Journal of Vacuum Science & Technology B published this new rapid and sensitive test [69], it

uses a technique that amplifies the binding signal for a target biomarker in a sophisticated way. The biosensor strip looks similar to glucose test strips with a small microfluidic channel at the tip to apply test fluids. A few electrodes are exposed to the fluid, Within the microfluidic channel which are coated with gold, and COVID-relevant antibodies are already attached to the gold electrode surfaces. The sensor strips are connected to a circuit board via a connector. A low-level electrical current flow between the gold electrode coated with COVID-19 antibody and the electrode. This signal is then returned to the circuit board for analysis. The strips can be discarded after use, but the circuit board is reusable. This recently developed technology is highly cost-effective and portable.

FLU SC2 Multiplex Assay, a different types of PCR test which can detect any of three respiratory viruses simultaneously: the COVID-19 virus, influenza A and influenza B (flu). Only a single test helps to determine three viruses, was recently developed [70]. The assay provides a sensitive, nucleic acid-based diagnostic tool for the evaluation of specimens from patients in the acute phase of infection. On July 2, 2020 the US Food and Drug Administration (FDA) granted Emergency use Authorization (EUA) for this test [71]. Symptoms shared between the two infections, Influenza and COVID-19, include chills, fever, difficulty breathing, cough, fatigue, body aches, diarrhoea and vomiting. COVID-19 spreads more rapidly and is often more severe. Only multiple assay testing can differentiate the two. This new Multiplex PCR contains multiple primer sets in a single PCR mix and produces amplicons which are of different sizes and sequences [72]. Although expensive and labour-intensive, this new method can quickly pinpoint agents responsible for acute respiratory infections.

A new bioluminescence testing method was recently developed in the Netherlands. It is a point-of-care antibody-based testing method that detects specific viral proteins. The existence of antibodies in the blood reflects that person was infected with the corona virus and had a past immune response. The sensor in this method works based on bioluminescence. If a certain protein or antibody is present in the sample, specific luciferase enzymes will emit light. When the device contains no biomarker of interest, one type of luciferase enzyme emits green light, but when a sample containing target biomarkers, a second luciferase enzyme that holds the key to detection will work [73]. Another research team in Japan has developed a rapid, cost-effective platform for quantitative antibody detection that also uses bioluminescent proteins, cotton threads, and a smartphone [74]. This detection method takes roughly 30 minutes time for complete. The sensitivity of this method ranged from 84.0% to 97.6%.

Another lab-on-chip testing technique is a new method that was recently developed in Singapore, where all required RT-PCR reagents are stored on a microchip. The whole process can be programmed to add them to a micro reaction chamber alongside a patient's biological sample with SARS-CoV-2 viruses to fulfil each PCR step. This technology is known as VereCoV [75]. This test is used in conjunction with VerePLEX bio system, and the test results can be used as supplementary data for diagnosis. A negative result does not preclude SARS-COV-2 infection and should not be used as a sole basis for treatment or other patient management decisions when this method is being used. Testing with VereCoV One Mix Detection kit is intended for use by trained laboratory professionals who are proficient in using the VerePLEX biosystem, which is another limitation.

A different types rapid detection method evolved that merges the PCR test steps and allows direct testing of the crude patient sample. Instead of RNA purification, in this method added inhibitor-resistant enzymes, which target the specific compounds that obstruct RNA amplification, such as mucin (a main component of mucus in the respiratory tract). So, this method reduces the inversion time from sample collection and also removing the need for the RNA purifying chemicals. This method is speedy, cost friendly and the availability of enzymes and reagents are obtainable, have high resistance to mucin-like inhibitor compounds that generally inhibit PCR reactions, rendering the regular PCR tests inaccurate sometimes. The biochemical mix of crude sample and inhibitor-resistant enzymes and reagents are transfer in a single tube, then it inserted into a laboratory thermocycler, a machine that is used to amplify genetic materials [75]. This upgraded PCR testing method capitulate results in just 36 minutes which is a quarter of the time of existing gold-standard RT-PCR tests. Not only COVID testing, this method can also be used to measure other viruses and bacteria, including the dengue virus.

4. CONCLUSIONS

We have discussed some newly emerging diagnostic methods which could be more specific, accurate, and cost-effective than RT-PCR. Because some of these methods are less expensive so they can be and should be used in developing and underdeveloped countries, especially with a high population. CRISPR-based FELUDA, SHERLOCK, Hyris kit, and COVIRAP are low time consuming, user friendly, and very appropriate for low-resource countries. The completion time durations for testing could be critical in emergencies and could help save a life. Chest CT scan is also an important tool for detecting Covid related respiratory syndrome, which is already very popular in recent clinical practices. CT-Scan is also an efficient detection tool for post covid complications. RT-LAMP is a contemporary technology with 97.5% sensitivity and 99.7% specificity and better than current RT-PCR, and it can be used in every country, including both low and high economies. An aptamer-based method is a highly promising technology being used for SARS-CoV-2 detections, but this method is still under developmental processes. Next-generation sequencing is an advanced technology with reasonable accuracy, and it can be used in developed countries with lower populations in moderate budgets. Despite all these recent developments, we believe there is still an urgent need to develop more practical, precise, and accurate detection test methods for SARS-CoV-2 and other emerging pathogens for protecting the global population.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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