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Paper-Based Biosensors for Management of Emerging Infectious Disease: A Brief Review

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Abstract: The current worldwide challenge is emerging infectious illness. The pandemic's billions of infected cases necessitate an emergency response to contain the outbreak. An early diagnosis and rapid treatment is a crucial idea for managing the outbreak. In order to diagnose growing infectious diseases, new biosensors are being developed as new therapies that are hoped to aid in accurate diagnosis. The materials for development of new tools for using as new infectious disease detection biosensors are extremely interesting topic in clinical material science. Good sustainable material is accepted for development of the new biosensor. The authors summarize and analyze sustainable materials and emerging infectious disease detection biosensors in this brief study, with a particular focus on COVID-19 and Zika virus infection. In this review, the paper-based biosensor for the "management of emerging infectious disease is summarized and discussed. Specific examples on COVID-19 and Zika virus disease are provided in this article.

Keywords: Emerging infectious disease, sustainable material, biosensor, paper

1. Introduction

Emerging infectious diseases are important medical problem. The operative definition of emerging infectious disease is an outbreak or occurrence of previously unknown infectious diseases or known diseases that have rapidly increased in incidence or occurred in new geographic range, and infectious diseases that cannot be controlled, according to the National Institute of Allergy and Infectious Diseases [1,2]. Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), Ebola, chikungunya disease, bird flu, swine flu, Zika virus disease, and most recently coronavirus disease 2019 (COVID-19) are among the 40 infectious diseases discovered since the 1970s [3,4].

The pandemic cause millions of infected cases, hence, there is a requirement for an emergency response to contain the outbreak. An early diagnosis and rapid treatment is a crucial idea for managing the outbreak. In order to diagnose growing infectious diseases, new biosensors are being developed as new therapies that are hoped to aid in accurate diagnosis [5]. Given the similarities in clinical presentation, point-of-care (POC) testing is helpful in the early identification of the etiological pathogen [5]. The materials for development of new tools for using as new infectious disease detection biosensors are extremely interesting topic in clinical material science. The authors summarize current data on using paper-based material as a sustainable material in new infectious disease detection biosensors in this brief review, with a particular focus on Zika virus disease and COVID-19.

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2. Sustainable Materials and Emerging Infectious Diseases Detection Biosensor

There is a lot of effort going into studying and preventing the spread of infectious diseases. Biosensors are an appealing technology that has the ability to detect a viral or illness outbreak. Despite the availability of a variety of technologies, both commercially and in the scientific literature, biosensor development for the diagnosis of emerging infections is still in its early path. The contemporary concept of sustainable materials is in line with the current trend of green and environmentally friendly technology. Simply put, sustainable materials are materials, which is producible in adequate numbers without reduction of non-renewable resources or disrupting the surrounding environments and main natural resources established steady-state balance. For early detection, biosensors are used.

Indeed, there are several kinds of sustainable materials that can be used for development of biosensor. However, the current review focuses on paper-based material, which is the most commonly use material in POC testing for clinical diagnosis [5]. In general, a paper-based biosensor, as an electrochemical biosensor, might be a non-composite or a composite made with other non-sustainable materials. However, in clinical medicine, a paper-based biosensor is usually a non-composite. Also, as earlier mentioned, the paper - based biosensor is the most common kind for the POC testing for clinical diagnosis of infection [5].

Microfluidic paper-based analytical devices (PADs) have a lot of promise because they are cheap, not difficult to use, quick, precise, and long-lasting in a range of conditions [5]. The application of green synthesized nanomaterials in optical biosensor devices is a current advanced technology. It can lead to a long-term and environmentally friendly COVID-19 solutions [7]. Using green synthesized materials in optical biosensor devices could lead to more ecologically friendly and sustainable solutions to the problem [7]. The sustainable material-based technology is one of the techniques worth considering. Paper-based biosensors for emerging infectious disease Detection is an example of a material-based technology that is currently very important [9]. Paper-based biosensors might be grouped by its approach (Table 1).

Table 1 - Advantages and disadvantage of different forms of biosensors for emerging infectious disease

Group	Advantages	Disadvantages
Nucleic acid detection	• Specificity is high and this technique is used as a diagnostic referencing technique.	• Cost is usually higher than the other forms. • Detection of previous infection is not possible.
Antigen detection	• Detection of current infection is possible.	• Detection of previous infection is not possible. • The false positive due to cross antigen reaction is possible.
Antibody detection	• Cost is usually lower than the other forms. • Detection of previous infection is possible.	• False negative is possible in case of early infection that immune response is not complete. • The false positive due to cross antibody reaction is possible.

The first group is paper-based biosensors for sensing for ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) of pathogen. Lateral flow assay (LFA) has emerged as a promising tool for creating portable, low-cost diagnostics that do not require specialist laboratory equipment or qualified staff [5]. This comes after the extensive research and development of LFA technology. After early proof of concept in the development of highly selective biochemical sensing techniques, Nitrocellulose based LFA test were utilized to detect the genetic component of the pathogen. In response to pandemic diagnostic needs, emerging biosensing technologies based on genetic material amplification with additional gene editing approaches have arisen, gaining significant acceptance in both research and clinical settings.

The second group is paper-based sensors for sensing for pathogen antigen. An alternative way for identifying pathogen is to look for pathogen-specific antigens. Basically, "antigen" is a protein of the pathogen that induces response and is related to the antibodies production. The early detection and diagnosis of infection is possible by detection of the antigen. Biosensors that target the antigenic protein in relevant body fluids can help detect infection. In the case of antigen detection, diagnose infection prior to the onset of symptoms and the occurrence of immune response is possible [8-10].

The third category is paper-based diagnostic tool for detection of pathogen immunogenic response. When a pathogen interacts with the human body, an immunogenic response to viral antigens emerges, which evolves over time as the virus progresses from asymptomatic to symptomatic to convalescent [8-10]. As part of the immunological response monitoring against pathogen, antibodies specific for the pathogen, principally immunoglobulins IgG, IgM, and IgA, are identified and quantified. Detection of antibodies by serological method is important in the control of the outbreak of infection. Now that mass immunization against COVID-19 is underway in several countries and the

monitoring of antibody is a useful indication [8-10] because it is applicable as a diagnostic tool for current and past infections. It is also useful and aid in better monitoring population immunity. The antibody detection biosensor basically combines the principles of basic immune recognition reactions and thin-layer chromatography to construct the diagnostic tool in a strip form. It can provide a rapid clinical diagnosis with an inexpensive visual transduction technique in a short period [5]. At present, LFA test strips appear to be a promising option for immunogenic response monitoring [5].

The disadvantages and advantages of each form of biosensor are different as presented in Table 2. The development of new diagnostic biosensor platforms with increased performance would, without a doubt, contribute to the control of the disease outbreak by enabling for early detection at the POC mean [7-10].

Table 2 - Advantages and disadvantage of different forms of biosensors for emerging infectious disease

Group	Details
Nucleic acid detection	This group detects the nucleic acid of the pathogen. Hence, it is accepted as a gold standard in clinical medicine at present [5].
Antigen detection	This group detects the antigen of the pathogen. Hence, it detects a component of the pathogen. However, the antigen is a protein which is coded from nucleic acid, hence, the diagnostic sensitivity of the test is not comparable to nucleic acid detection [5].
Antibody detection	This group detects the antibody against pathogen. Hence, it detects the immune response. There might be a problem of false negative in case that the immune response does not completely occur [5].

3. Paper-Based Biosensors and Diagnosis of COVID-19

COVID-19 is an emerging infectious disease. This emerging infection is caused by the new coronavirus that can cause a severe acute respiratory syndrome. The causative pathogen is severe acute respiratory syndrome virus-2 (SARS-CoV-2). The first reported case was detected in East Asia in December of 2019. The disease has since spread around the world, resulting in a pandemic [10]. COVID-19 is a virus that causes a respiratory infection. COVID-19 symptoms include febrile illness, cough, cephalgia, fatigue, breathing trouble, loss of taste and smell. After being exposed to the SARS-CoV-2, the mentioned clinical symptoms might occur anywhere from one day to two weeks [10-16].

The COVID-19 outbreak still continues and management in containing the outbreak cannot be overstated. COVID-19 is usually suspected through symptoms and then confirmed using nucleic acid tests of infected secretions. A gold standard test at present is based on reverse transcription polymerase chain reaction (RT-PCR). In persons with a high clinical suspicion of infection, chest CT scans, in addition to laboratory tests, is useful for diagnosing COVID-19. Serological test is available to determine a past infection by identifying specific immunoglobilines produced by the body reaction to SARS-CoV-2 infection [21-27]. The new biosensors are being used to diagnose COVID-19, and it is believed that they will help with more accurate diagnosis. In clinical material science, the challenges posed by materials for COVID-19 detection biosensors are fascinating.

As previously stated, early detection of infection is required for a successful COVID-19 control. A prompt and consistent laboratory detection of active SARS-CoV-2 infection is a key point to be considered in COVID-19 outbreak control. It might be difficult for a non-specialist to use the appropriate specimen type and laboratory-diagnostic technique in the relevant clinical circumstance because there are so many tests on the market [19]. The possible clinical role of blood and feces specimens, as well as the disparities in diagnostic performance between lower and upper respiratory tract specimens, are discussed [19].

Because asymptomatic SARS-CoV-2 infection and carrier status is possible and not uncommon, early and accurate diagnosis is crucial for disease control and further prevention of spreading of disease. When utilized together, both CT tests and RT-PCR would improve diagnostic sensitivity [20,21]. As a result, an appropriate quarantine efficacy, something neither could do alone [20,21]. The clinical efficacy of many of the technologies and procedures used to diagnose COVID-19, as well as methodology established by various research institutes and commercial devices and kits for the SARS-CoV-2 detection, largely varies. The merits and limitations of the current approaches are highlighted after a description of the current methodologies [21].

The spreading of pandemic is rapid over the world. Despite substantial efforts to contain and manage the problem, it remains widespread in a number of countries, with different degrees of clinical symptoms. To manage the pandemic, a good collaborative approach that includes epidemiology surveillance, accurate diagnosis and appropriate prophylactics are necessary. On the other hand, proper diagnosis using rapid technology is crucial [20-22]. With the increased number of COVID-19 incidences, accurate and prompt SARS-CoV-2 infection identification is essential for effective prevention and management, as well as restricting the virus's dissemination. The RT-PCR assay is considered

the gold standard in laboratory medicine, but it has limited application as a bedside diagnostic due to its technical complexity [22]. Many POC assays have been developed to assist in COVID-19 diagnosis outside of centralized testing laboratories and to speed up clinical decision-making with the lowest feasible turnaround time to address these difficulties [22].

The most commonly utilized and approved technologies now accessible include immunoenzymatic serological test, rapid antigen or antibody tests, and RTPCR-based molecular diagnostic tests. Other techniques, such as clusters of regularly interspaced short palindromic repeats/Cas (CRISPR/Cas)-based approaches, isothermal nucleic acid amplification, or digital PCR methods, are now being used in clinical research settings. Most are awaiting approval by competent authorities for diagnostic usage [23]. Some paper-based biosensor for detection of SARS-CoV-2 RNA is available [22], however, the cost is usually high comparing to the other forms of paper-based biosensor for COVID-19 diagnosis. Therefore, almost all currently use biosensors for diagnosis of COVID-19 are antibody or antigen detection forms [20–22]. Nevertheless, the paper-based biosensor for detection of nucleic acid is still accepted as a clinical diagnostic referencing standard with a high specificity [20-22].

The antibody and antigen detection biosensor are usually inexpensive and can provide a rapid result, therefore, the POC testing is possible and can allow rapid disease control [5]. Antibody test can help detect either past or present infection based on specific immunologlobulin determination. However, the problems of false negative in early infection or window period and false positive due to cross reaction (such as to dengue) are possible [20-22]. Regarding antigen detection, the similar problem of false positive due to cross reaction (such as to non-SARS-CoV-2 coronavirus) is also reported [20-22].

Newer, more efficient methods for detecting viral analytes quickly are required, taking into account viruses' flexibility and reproduction habitats. These approaches must be applied in such a way that they offer improved accuracy, broad-scale availability and easy – to- move in order to test a huge population [24]. The development of new COVID-19 biosensors that are rapid, reliable, and sensitive has sparked a lot of interest [24-25]. These biosensors would be a one-step identification or sensing method that do not require separation (nucleic acid extraction), incubation, and signal-reporting agents. COVID-19 biosensors are extremely selective and rely on surface nucleoproteins that connect to internal genetic material and angiotensin-converting enzyme 2 (ACE-2) receptor of the host. Biomarkers other than antibodies or immunoglobulins could be detected in human hosts. As earlier note, the different forms of paper-based biosensor for diagnosis of COVID-19 are presently available [27]. Each form has its specific advantage and disadvantage as already mentioned in Table 2.

Currently, there are many commercially available COVID-19 test [28]. The urgent development of the test is to correspond the ongoing COVID-19 pandemic [29,30]. The simple and fast diagnosis is the main aim of the development. Many new POC assays for COVID-19 diagnosis is available. The emerging important consideration is the quality of the newly launched commercial COVID-19 POC test [31,32]. It is a basic rule that there must be a quality control of the test and the local public health governmental body has to set a system for controlling the standardization of the available test. For each specific laboratory that applies the newly available biosensor, a validation and comparison of the new test to the standard diagnostic test is required.

Of several types, the antigen test is generally used since it does not require a complex procedure (which requires in nucleic acid sensing) or an invasive sample collection procedure (which requires in antibody sensing based on serum) [33,34]. Comparing to other kinds of biosensors, paper-based LFA is currently widely used due to its convenience. It can provide a fast result and can help early diagnosis of COVID-19. Since the analytical procedure of the LFA is usually simple, it is possible to perform the test on site as a POC test. Additionally, the paper based LFA might be performed by general people [27]. During the COVID-19 outbreak, the local public health policies in many settings presently promote self-testing by using paper - based LFA. The self-test for COVID-19 can help increase number of detection rate for asymptomatic and mild COVID-19 cases (Fig. 1).

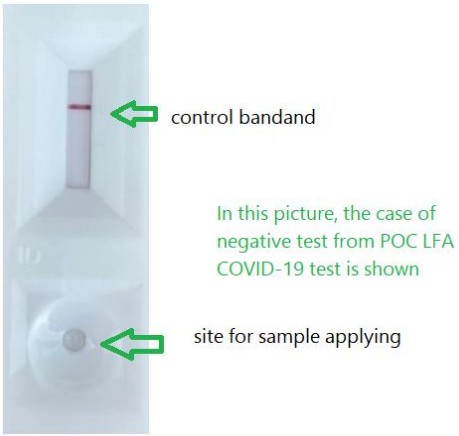

Fig. 1 - Example of paper based LFA for diagnosis of COVID-19

Regarding the available LFA for COVID-19 diagnosis, the control of using is needed. It is necessary to have a specific guideline for the user on how to perform the test, how to control the quality of the test and how to interpret the results. Reference manual must be provided in each commercially available paper-based POC assay [27,33,34]. At present, the simplest LFA for COVID-19 test is based on a one step sample applying and the result can be derived within a few minutes. The reading of the result is by naked eye and the line appearance is used for interpretation.

Since there is an interesting use of paper-based LFA for COVID-19 diagnosis, the sustainable material can help decrease the problem of hazardous waste management., Comparing to other materials such as plastic materials, the paper is easier to destroy and spontaneous degradation is possible [33,34].

Finally, it should mention for the weakness of the paper-based diagnostic assay. The good keep of the sensor is necessary since an extreme high temperature of too much humid environment might cause the decreasing quality of the tests [33,34]. Therefore, an important concern before using the sensor is the checking for its condition and this might be simple for the case of commercially available LFA that usually labels for expiration date.

4. Paper-Based Biosensors and diagnosis of Zika virus infection

Zika virus sickness is caused by an arbovirus. The pathogen is transmitted by Aedes mosquitoes that bite during the daytime. Fever, headache conjunctivitis, skin rash, joint and muscle discomfort are common clinical symptoms. The clinical symptoms usually last for 2–7 days. The majority of those infected with the Zika virus do not experience any symptoms. Congenital Zika syndrome is caused by maternal Zika virus infection during pregnancy. The maternal infection can result in infection in infants. Affected infants are born with microcephaly and other congenital defects. Maternal Zika virus infection is also linked to various pregnancy concerns such including miscarriage and preterm delivery. Fever, headache, skin rash, arthralgia, red eyes, and muscle soreness are the most prevalent clinical symptoms, as previously stated. Zika is transmitted mostly by the bite of an infected mosquito. Avoid mosquito bites is a basic rule to avoid Zika [25-34].

The disease has quickly spread and becomes a global public health problem. Despite substantial efforts to contain the disease, it remains widespread in a several areas of the world, with a wide range of clinical symptoms. This pandemic will require a collaborative approach that includes accurate disease investigation, good outbreak surveillance, and prevention. On the other hand, accurate diagnosis using cutting-edge technology is crucial. The new Zika biosensor's speed, sensitivity, and selectivity make it an attractive candidate for development as a medical laboratory analytical tool. During an outbreak, the use of a paper-based POC sensor for Zika virus detection can solve the problem of the requirement for refrigeration during specimen transport and storage, allowing for Zika virus surveillance in resource-limited settings. In addition, the design is adaptable (interchangeable recognition element [35]. In resource-constrained contexts, the suggested paper-based extraction and detection platforms could be used to diagnose infectious viral infections from complex clinical samples [35].

Nevertheless, there are many current available biosensors for Zika virus disease detection comparing to other neglected tropical infections [36]. Like COVID-19, most available biosensor is made of paper-based material. Most biosensors are for antibody detection. Advanced combination with smartphone technology for online detection of Zika virus disease is already available [37]. However, the nucleic acid identification form of biosensor is still the most reliable tool and accepted as gold standard [39,40]. The nucleic acid-based biosensor for Zika virus disease can help detect pathogen not only in clinical sample but also environmental sample [38]. Nevertheless, a more complex biosensor targeting on multiple pathogens is also continuously developed. A good example is the new paper-based sensor for clinical diagnosis of f zika, dengue, and chikungunya virus using nucleic acid detection [39,40]. As earlier note, the different forms of paper-based biosensor for detection of Zika virus disease are presently available. Different form of biosensor has different specific advantage and disadvantage as already mentioned in Table 2.

5. Conclusion

Emerging infectious illness is a major global concern right now. Because of the pandemic's billions of infected cases, fast action is required to keep the outbreak under control. It is impossible to stress the importance of early detection and treatment in controlling an outbreak. The development of novel developing infectious disease biosensors that are quick, accurate, and sensitive has piqued attention. These biosensors would allow for one-step identification and sensing. Biosensors have already shown that they can give a cost-effective and easily accessible diagnostics in situations where traditional laboratory techniques are unavailable. Because of their recyclability, ability to mass-produce using sustainable methods, and safe disposal, paper and cellulose-based sensors are specifically beneficial in pandemic scenarios. Sustainable materials are a modern concept that fits in perfectly with the current green and ecologically friendly technological trend. Green nanoparticles could be employed in optical biosensors to provide better long-term and environmentally friendly solutions to the problem of infectious disease development.

The advantages of each form of paper-based biosensor include a feasibility to allow rapid POC diagnosis of the emerging infectious disease which is a key point for management of the outbreak situation. Specific approach on pathogen, antigen and antibody detection can help practitioner to early diagnose of the disease. Comparing to the older techniques, although the pathogen, antigen and antibody detection might be possible but it usually non convenient. The

paper-based biosensor is usually smaller and cheaper for development. Additionally, there is a less problem of waste after usage in case of paper-based biosensor. However, there might be some disadvantages of paper-based biosensor. The nature of paper might require a good environmental control to prevent the paper-based biosensor from humidity or chemicals that might deteriorate the function of the biosensor. At present, paper-based techniques become widely and proven useful to correspond the current emerging infectious disease pandemic situation. It necessary to devote more attention to the management of paper-based techniques than to the traditional method since paper-based techniques are currently implemented worldwide aiming at rapid diagnosis of the infection that can allow prompt management of disease and control of spreading. The management and quality control of the techniques are necessary to assure the correctness of analysis that can further affect the management of the pandemic situation. According to this review, it is recommended that continuous research and development on paper-based techniques are required and there should be a reappraisal on the current available paper-based techniques to look for the point for continuous improvement. Additionally, there should a reappraisal on the situation to gather lesson learnt for the future.

Conflict of Interest

The authors declare that there is no conflict of interest

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