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Paper-based devices for rapid diagnosis and wastewater surveillance

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ABSTRACT

Infectious diseases are a global concern for public health resulting in high rates of infection with subsequent health and socio-economic impacts through resulting morbidity and mortality. The emergence of such diseases has motivated researchers to develop cost-effective, rapid and sensitive analytical methods and devices to better understand the transmission routes of infections within populations. To this end, rapid and low-cost diagnosis and testing devices for infectious diseases are attracting increasing amounts of attention, e.g., through using paper-based analytical devices (PADs). In this paper, the recent development of PADs is critically reviewed both for the diagnosis of inviduals and population health, by using devices for testing wastewater. Finally, the review also focuses on PADs for the analysis of bacteria and viruses in wastewater, together with a discussion on thee future development of PADs for rapid diagnosis and wastewater surveillance.

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1. Paper-based analytical devices

Paper-based analytical devices (PADs) were first introduced in the 20th century, which depended on power-free fluid transport by capillary action. By using photoresist for fluid control, Whitesides et al. [1] first demonstrated their devices as microfluidic paper-based analytical devices (μPADs), as an economical, portable and disposable platform for various biomedical sample types. Later, the same group developed wax-printed μPADs for colorimetric analysis. In 2009, Henry et al. [2] proposed an electrochemical paper-based analytical device (ePAD) to improve the quantitative analytical performance of μPADs. To make full use of the hydrophilic properties, the choice of paper substrate is of great importance with hydrophobic barriers usually being created on paper substrates to restrict lateral fluid flow.

Paper or paper-like cellulose materials are an essential material for PAD fabrication. As a substrate material, paper shows significant advantages including uniformity in structure, affordability, accessibility, user-friendliness, and affinity of the fiber surface for different analytes. Paper also possesses a porous hydrophilic structure, and can drive fluid flow through capillary force without the need for external microfluidic pumps or associated equipment. Moreover, the hydrophobicity and reactivity of the paper can be changed by altering its chemical structure. It is important to highlight that the applications of PADs mainly depend on the characteristics of the paper, including composition/material grade, size, thickness, pore size, roughness and porosity [3]. A suitable paper substrate must be selected to optimize or enhance the specificity and sensitivity of target analysis.

At present, various paper substrates with different characteristics have been used to construct PADs, including unmodified cellulose paper such as filter paper, chromatography paper, blotting paper, office paper, art paper, and functional paper such as graphene paper and graphite paper [4–6]. In addition, paper-like materials including nitrocellulose membrane, polyvinylidene fluoride (PVDF) membrane, and mixed cellulose ester (MCE) membrane can also be used. Among them, filter paper, due to its high porosity, can provide a high surface area to absorb reagents for biochemical reactions, so it is extremely popular in manufacturing PADs. Whatman Grade 1 Chromatography Paper is one of the most

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commonly used chromatography papers because of its uniform structure, good hydrophilicity and smooth surface. When it comes to the construction of ePADs, bare cellulose paper shows the limitation of poor conductivity when used in electronic PADs [7]. Compared with unmodified cellulose paper, conductive paper provides larger surface area and more superior electrocatalytic activity, thereby enhancing the sensitivity and selectivity of ePADs.

The fabrication of PADs is mainly based on the manufacture of hydrophobic barriers on paper substrates. This concept was first realized by lithography in 2007 [8], and the researchers used chemical photoresist to create hydrophobic barriers on paper substrates by exposing paper substrates to light passing through photomasks. Although this method provides good resolution, the fabricated PADs are relatively brittle and accompanied by background signal interference [9,10]. So far, researchers have proposed a variety of fabrication methods, such as three-dimensional (3D) printing, wax printing, wax jetting, screen printing, inkjet printing, permanent marker pen and scholar glue spray method [11–13]. It must be mentioned that most fabrication methods require benchtop instruments (e.g., printers, hot plates and ovens) and additional steps (e.g., printing, heating and spraying).

For PAD fabrication, wax is the most common barrier material due to its ability to generate excellent hydrophobic and hydrophilic regions. Wax printing is a simple, cheap and environmentally friendly technique to form high-resolution patterns for mass production. Screen printing is another popular technology for printing hydrophobic barriers on paper substrates due to its ultra-stable performance and excellent repeatability. However, expensive precision instruments for manufacturing templates and complicated manufacturing procedures prevent the widespread use of Screen printing. Recently, pen-based fabrication strategies have been used to create hydrophobic barriers and conductive traces on paper substrates to meet the needs of on-site design. Customized crayons, technical drawing pens and permanent marking ink pens are employed to construct hydrophobic barriers [14], while pencils, ballpoint and fountain pens are applied for the manufacture of paper-based electrodes. In addition, cutting is used in PAD manufacturing to form flow channels without changing the chemical properties of paper substrates.

In the past decades, a number of researchers have reported the applications of PADs, involving food safety, clinical diagnosis, drug development and environmental monitoring [15–18]. The market-oriented commercialization of reliable and affordable PADs for rapid diagnosis and wastewater surveillance remains to be explored, and cooperation between academic institutions, medical departments and manufacturing industry is essential. Herein, this review presents an overview of the applications of PADs. PADs for infectious disease diagnosis are introduced, including multiplexed detection of infectious diseases. PADs for the analysis of bacteria and viruses in wastewater are then presented. Finally, the challenges and perspectives of PADs for rapid diagnosis and wastewater surveillance are discussed.

2. Infectious disease

Infectious diseases have currently placed a significant burden on global public health, causing tens of millions of deaths each year. To reduce infection and mortality rates, it is essential to perform early diagnosis and implement timely treatment. Conventional diagnostic methods for infectious diseases include using microscopes, microbial culture, western blots, blood tests, nucleic acid amplification tests (NAATs) and immunodiagnostics, most commonly involving enzyme-linked immunosorbent assay (ELISA) [19]. To realize rapid and effective NAATs, different techniques including polymerase chain reaction (PCR), quantitative PCR (qPCR) and isothermal methods such as loop-mediated isothermal amplification (LAMP) have been reported. Although these techniques can offer reliable diagnosis, they often require laboratory facilities, expensive equipment, experienced technicians. Often diagnostic workflows are complexed, limiting their applications for on-site diagnosis at low resource settings. Therefore, low-cost, rapid, accurate and user-friendly diagnostic platforms are critical for infectious disease diagnosis.

PADs provide a promising solution for infectious disease diagnosis, with the advantages of affordability, speed, high sensitivities and specificities as well as simplicity in their use. In recent years, due to the great demand for on-site testing in low-resource communities, PADs have received considerable critical attention. To date, there have been various substrate materials used for PAD fabrication. Different fabrication methods have been established to build hydrophobic barriers on paper substrates. PADs have been applied for colorimetric, chromatographic, electrochemical, fluorescent, electrochemiluminescence (ECL), immunochromatographic assay (ICA) and surface plasmon resonance (SPR) diagnosis of numerous infectious diseases [20,21]. In addition, microfluidics, electronics, biotechnology, nanotechnology and material science have been explored to accelerate the development of PADs for point-of-care (POC) applications.

3. Paper-based analytical devices for rapid diagnosis

The World Health Organization (WHO) describes infectious diseases as resulting from pathogenic microorganisms, like bacteria, viruses, parasites, or fungi [22], and can be transmitted from person to person directly or indirectly. There are also many documented cases of zoonotic with animal-human transmission and vice-versa [23].

It is estimated that around 15 million deaths are directly associated with infectious diseases [24]. Generally, more than 95% of infectious disease deaths result from the lack of appropriate medical facilities, diagnosis and treatment [25]. Therefore, early diagnosis and effective treatment of infectious diseases are necessary. The 'REASSURED' (real-time connectivity, ease of specimen collection, affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free or simple environmentally friendly, and deliverable to end-users) guidelines announced by WHO play significant roles in developing suitable methods for infectious disease diagnosis at low-resource settings [26].

As stated by the National Institutes of Health, a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [27]. Biomarkers have been used as measurable indicators to detect various disease specific analytes (e.g., nucleic acids, proteins, metabolites and unusual entities) in clinical diagnosis and health monitoring [28]. Diagnostic biomarkers can be used to assess disease status, and prognostic biomarkers can inform disease outcomes. Host biomarkers in infectious diseases have also attracted much attention, which can help assess the efficacy of vaccines and understand the molecular mechanisms of potential infections [29]. Therefore, the detection of accurate, noninvasive and user-friendly biomarkers are significant in the screening, diagnosis, prognosis and therapy of infectious diseases. Recent developments in PADs have led to an increasing interest in infectious disease diagnosis, which will help prevent and control the spread of diseases.

3.1. Paper-based analytical devices for infectious disease diagnosis

Most morbidity and mortality related to infectious diseases appear in the developing countries with limited medical resources.

Hence, affordable, accurate and user-friendly methods for infectious disease diagnosis are indispensable to decrease the burden of infectious diseases on global health. With the prominent advantages over conventional methods, PADs have been applied for infectious disease diagnosis. This section discusses the applications of PADs for rapid diagnosis of infectious diseases such as tuberculosis (TB), malaria, acquired immunodeficiency syndrome (AIDS), dengue, Ebola, hepatitis, influenza, zika, norovirus and coronavirus disease 2019 (COVID-19) (Table 1).

Various types of bacteria exist in the human intestine and are excreted within the feces. Enteric bacterial pathogens often cause gastrointestinal infections including diarrhea and gastroenteritis. With the overall goal of providing a faster response and lower cost detection tool than conventional methods, many researchers have introduced PADs that can detect various types of bacteria, such as *Escherichia coli* (*E. coli*) [30–32], *Enterococcus* species [33], *Salmonella* Typhimurium (*S. typhimurium*) [34], *Listeria monocytogenes* (*L. monocytogenes*) [35], *Vibrio cholerae* (*V. cholerae*) [36], *Pseudomonas aeruginosa* (*P. aeruginosa*) [37], *Chlamydia trachomatis* (*C. trachomatis*) [38], *Enterobacter sakazakii* (*E. sakazakii*) [39] and *Vibrio vulnificus* (*V. vulnificus*) [40].

The most common technique applied to PADs is colorimetric analysis, which is usually based on the interaction between bacteria and recognition elements that lead to chromogenic products. Although colorimetric PADs can function with various quantum dots, soluble dyes and redox-active nanoparticles, they may also suffer from poor selectivity and difficulty in making quantitative measurements. For example, a chromogenic medium embedded in PAD was established to detect *V. cholerae* in canal, river, sea, spring and hand pumpwater [36]. Although the PAD is a potential strategy for *V. cholerae* detection in resource-poor areas, it still took 18–24 h to complete the entire process. In another work, a paper-based platform based on cheap graphite pencil leads was tested to detect *P. aeruginosa* cells by measuring pyocyanin (PYO) concentrations (Fig. 1a) [37]. By square-wave voltammetry (SWV) analysis, the device showed a linear response to PYO in the range of 50–1000 nmol L^{-1}. The platform was employed to evaluate related species with 200-fold higher levels of PYO in human biofluids, confirming the platform's excellent selectivity.

In addition to colorimetric and electrochemical analysis, photoluminescence analysis was also applied for PADs. Cheeveewattanagul et al. [31] presented a nanohybrid material based on graphene oxide-coated nanopaper (GONAP), which provided hydrophilicity, porosity, and photoluminescence quenching properties (Fig. 1c). The platform was used for *E. coli* detection in buffer, poultry and river water within 30 min, and the corresponding detection limits were 55, 65 and 70 CFU mL^{-1}, separately. Although GONAP provids a new strategy for food and environment monitoring, the specificity and sensitivity of the platform remain to be explored. Liu et al. [35] constructed a wireless paper bipolar electrochemical luminescence (pBPE-ECL) analysis system that could detect as little as 10 copies μL^{-1} of *L. monocytogenes* genomic DNA. The "optical switch" molecule $[Ru(phen)_2dppz]^{2+}$ was used to insert the base pair of the double-stranded DNA, and the complex

Table 1
Paper-based analytical devices for infectious disease diagnosis.

Detection method	Infectious disease	Biomarker	Substrate material	Fabrication method	Recognition element	Linear range	LOD	Sample	Ref.
Colorimetric	Malaria	PfLDH	Whatman 3 MM Chromatography Paper	Punch cutting	Aptamer	5 –5000 ng mL^{-1}	5 ng mL^{-1}	Blood	[48]
Colorimetric	Dengue fever	Dengue virus	Nitrocellulose membrane	Cut using a roller cutter	Antibody	4.9–25 ng mL^{-1}	4.9 ng mL^{-1}	Serum	[65]
Colorimetric	Influenza	pH1N1 nucleoprotein	Millipore PVDF transfer membrane	Cut using scissors	Antibody	–	5×10^3 $TCID_{50}$	Nasal fluid	[85]
Colorimetric	AIDS	HIV-1 RNA	Ustar Biotechnologies commercial LFIA	–	RT-LAMP primers	–	100 copies	Blood	[62]
Colorimetric	AIDS	HIV nucleic acid	Nitrocellulose membrane	Cut using Rapid Test Cutter ZQ2000	Detector probe	–	0.1 nM	Buffer	[118]
CV	Dengue fever	DENV DNA	Cellulose paper	Stencil printing	Probe DNA	100 pM-1 μM	100 pM	Buffer	[69]
DPV	Influenza	Influenza virus	Whatman Grade 4 Chromatography Paper	Spray coating and stencil printing	Antibody	113–10^4 PFU mL^{-1}	113 PFU mL^{-1}	Saliva	[86]
SWV	COVID-19	SARS-CoV-2 antibody	Whatman Grade 4 Chromatography Paper	Wax printing and screen printing	Spike protein	–	1 ng mL^{-1}	Sera	[107]
ASWV	Hepatitis	Hepatitis virus	Nitrocellulose membrane	Wax printing and screen printing	acpcPNA probe	10 pM-2 μM	7.23 pM	Serum	[80]
EIS	TB	MTB DNA	Whatman No.1 Filter Paper	Wax printing and screen printing	acpcPNA probe	2–200 nM	1.24 nM	Blood	[44]
EIS	Zika	Zika virus	Whatman 3 MM Chromatography paper	Screen printing	Antibody	10^2-10^5 copies μL^{-1}	10 copies μL^{-1}	Plasma, urine, and semen	[91]
Fluorescence	AIDS	HIV-1 p24 antigen	Whatman Grade 1 Filter Paper	Hand-printing using a wax pencil	Antibody	1 ng mL^{-1}-10 μg mL^{-1}	1 ng mL^{-1}	Plasma	[61]
Fluorescence	AIDS	HIV virus	Whatman Grade 1 Filter Paper	Hand-printing using a wax pencil	Antibody	250 pg mL^{-1}-10 μg mL^{-1}	250 pg mL^{-1}	Plasma	[61]
Fluorescence	Ebola	Ebola RNA	Whatman Grade 1 Chromatography Paper	Wax printing	RT-RPA primers	–	10^7 copies μL^{-1}	Plasma	[72]
Fluorescence	Norovirus	Norovirus	Nitrocellulose membrane	Wax printing	Antibody	1-10^4 copies μL^{-1}	1 copy μL^{-1}	Water and reclaimed wastewater	[98]
Fluorescence	Zika	Zika virus	PES membrane	Wax printing	RT-LAMP primers	–	5 copies μL^{-1}	Serum	[115]
ECL	Hepatitis	HBsAg	Whatman Grade 1 Filter Paper	Cut to size	Antibody	34.2 pg mL^{-1} –34.2 ng mL^{-1}	34.2 pg mL^{-1}	Serum	[76]
LSPR	Zika	Anti-ZIKV antibody	Whatman Grade 1 Filter Paper	Cut to size	NS1	–	1 ng mL^{-1}	Serum	[89]
Mie scattering	Norovirus	Norovirus	Chromatography paper	Wax printing	Antibody	10–10^7 pg mL^{-1}	10 pg mL^{-1}	Buffer	[93]

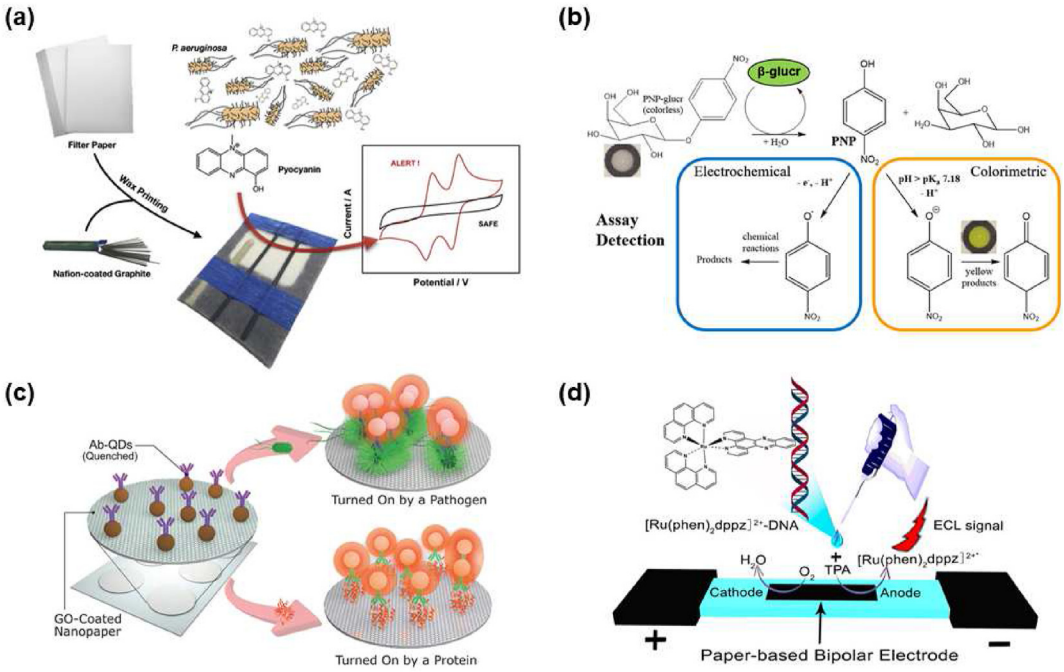

Fig. 1. Examples of PADs for bacteria detection, including (a) *P. aeruginosa*, (b) *Enterococcus* species, (c) *E.coli* and (d) *L.monocytogenes*. (reprinted from Refs. [31,33,35,37] with permission from Elsevier, American Chemical Society, and John Wiley and Sons).

was then applied to a paper-based bipolar electrode for ECL detection (Fig. 1d). The chip holds great promise for on-site analysis of bacteria by using a battery as a power source and a smartphone as a readout device.

The deadly bacterial pathogen *Mycobacterium tuberculosis* (MTB) is the causative agent of TB. According to the Global Tuberculosis Report 2019, around 10 million people were infected with TB in 2018 [41]. PADs have attracted extensive attention in TB diagnosis. MTB DNA have been determined by fluorescence analysis on Whatman Grade 1 Chromatography Paper [42], colorimetric analysis on Whatman Grade 3 MM Cellulose Chromatography Paper [43], and electrochemical impedance spectroscopy (EIS) analysis on Whatman No.1 Filter Paper [44]. In 2018, Teengam et al. [44] proposed a PAD for MTB DNA measurement in blood, with a linear range of 2−200 nM and a LOD of 1.24 nM (Fig. 2b). Specifically, the pyrrolidinyl peptide nucleic acid (acpcPNA) was covalently immobilized on Whatman No.1 Filter Paper and served as a probe to capture target DNA. Due to the conformationally constrained structure, acpcPNA probes are highly selective to complementary oligonucleotides, which highlights their potential in clinical applications.

Malaria is an infectious disease caused by *Plasmodium* parasites [45]. According to the World Malaria Report 2019, there were approximately 228 million cases caused by malaria in 2018 [46]. PADs have provided a promising platform for malaria diagnosis, which detected biomarkers including *Plasmodium* lactate dehydrogenase (pLDH) [47], *Plasmodium falciparum* lactate dehydrogenase (PfLDH) [48,49], *Plasmodium falciparum* histidine-rich protein 2 (PfHRP2) [50−52], and *Plasmodium falciparum* glutamate dehydrogenase (PfGDH) [53]. Singh et al. [53] presented a dye-based chromogenic PAD to detect pan malaria and *Plasmodium falciparum* (*P. falciparum*). The strategy not only employed the aptamer-coated magnetic beads to exclude the interferences from serum, but also helped avoid washing and drying fragile paper (Fig. 2a). Xu et al. [54] integrated DNA extraction, LAMP, and fluorescence detection on an origami paper device for the detection of *P. falciparum*, *Plasmodium vivax* (*P. vivax*) and *Plasmodium pan* (*P. pan*) from whole blood. Later, the paper-origami assay was developed for on-site detection in rural schools in Uganda [55], showing a sensitivity of 98% for malaria diagnosis. These devices have more recently been integrated into a mobile-health platform using a smart phone to power a simple circuit controlling the temperature during an isothermal LAMP amplification with a blockchain security used for end-to-end privacy of patient data [56].

In addition to bacteria and parasites, viruses are also causative factors of infectious diseases. Viruses include single-stranded or double-stranded RNA and DNA variants, and have external proteins called capsids. The protein contains one or more structural proteins and surrounds the viral genome. Viruses are usually transmitted through infected carriers, contact with contaminated objects and exposure to aerosol virus particles [57]. Numerous efforts have been undertaken to employ PADs to detect infectious diseases caused by viruses.

AIDS is an infectious disease caused by human immunodeficiency virus (HIV) [58]. Unprotected sexual behavior with HIV-infected partners, HIV-contaminated blood transfusions or infections from HIV-infected pregnant women to children remain the main transmission routes of AIDS [59]. Recently, PADs have been used to detect biomarkers in serum, plasma and blood, such as HIV-1 p24 antigen [60,61] and HIV RNA [62], for AIDS diagnosis. Because the reverse transcription polymerase chain reaction (RT-PCR) assay for HIV RNA is 3−5 days earlier than the HIV-1 p24 antigen assay, the former method is preferred. In one study, 39 serum samples were spotted on the filter paper for HIV-1 p24 antigen detection [60]. The sensitivity of the fourth-generation immunoassay, Determine™ HIV-1/2, and Liaison XL were 87.2%, 61.5% and 48.7%, respectively, indicating that fourth-generation immunoassays are more sensitive than rapid diagnostic tests in the early stages of HIV infection detection.

Dengue fever is caused by a positive-sense ssRNA virus dengue virus (DENV) [63]. DENV is mainly spread by mosquito vectors

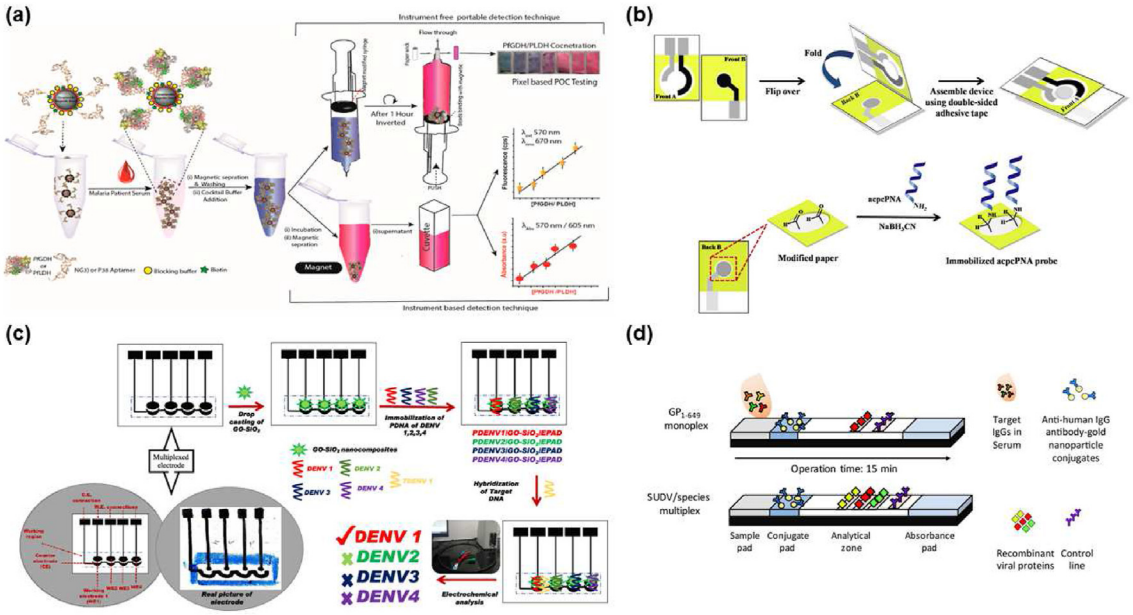

Fig. 2. Examples of PADs for infectious disease diagnosis, including (a) malaria, (b) TB, (c) dengue fever and (d) Ebola. (reprinted from Refs. [44,53,69,73] with permission from American Chemical Society and Elsevier).

including *Aedes aegypti* and *Aedes albopictus*. There are about 400 million dengue fever cases annually [64]. With advances in biosensing technology, PADs have been applied for detecting dengue non-structural protein 1 (NS1) [65–67] and DENV DNA [68,69] in Dengue fever diagnosis. Kumar et al. [65] established a lateral immunoassay based on nitrocellulose membrane and gold-reduced graphene oxide (Au-rGO) to detect dengue NS1. The tapered nitrocellulose membrane increased the concentration gradient of AuNPs at the test line to enhance the color intensity here. The LOD of this immunoassay was 4.9 ng mL^{-1}, which was lower than those obtained by a laser-cut μPAD made of glass fiber filter paper (25 ng mL^{-1}) [66] or by a wax-printed μPAD made of cellulose chromatography paper (46.7–200 ng mL^{-1}) [67]. Moreover, Singhal et al. [69] designed an ePAD for cyclic voltammetry (CV) analysis of DENV DNA based on the coated graphene oxide-silicon dioxide ($GO-SiO_2$) nanocomposites (Fig. 2c). The device showed excellent specificity for DENV serotypes including DENV 1, DENV 2, DENV 3, and DENV 4.

Ebola virus is a lethal pathogen that causes Ebola virus disease (EVD) with a fatality rate of up to 90% in humans [70]. The 2018–2019 EVD outbreak in West Africa stresses the importance of early diagnosis for EVD monitoring and control [71]. Recently, PADs have been used to detect biomarkers such as Ebola RNA [72] and EVD immunoglobulin G (IgG) antibodies [73], for Ebola diagnosis. Brangel et al. [73] reported a lateral flow test strip to detect EVD IgG antibodies in the serum samples of EVD survivors in Uganda (Fig. 2d). By using smartphone applications, the collected samples were measured semi-quantitatively, and attached with geographic tags. Furthermore, a multiplex strip was used to determine antibodies against three Ebola pathogens including ebola, sudan and bondi buji virus. With the advantages of lateral flow test strips and smartphone applications, the platform provides a convenient strategy for POC surveillance of survivors after Ebola outbreaks.

Hepatitis is an infectious disease transmitted among humans through contact with infected blood or body fluids, which can cause life-threatening diseases including cirrhosis, chronic hepatitis, and liver cancer [74]. In 2015, about 257 million people were infected with chronic hepatitis B virus (HBV), and 71 million people were infected with chronic hepatitis C virus (HCV) [75]. PADs have provided a promising platform for hepatitis diagnosis, which can detect biomarkers including hepatitis B surface antigen (HBsAg) [76,77], hepatitis B surface antibody (Anti-HBs) [77], hepatitis B core antibody (Anti-HBc) [77] and HBV DNA [78–80]. Akkapinyo et al. [77] tested both rapid testing and electrochemical analysis for hepatitis B diagnosis (Fig. 3a). They first produced AuNPs-based hepatitis B test strips that could simultaneously detect HBsAg, *anti*-HBs and *anti*-HBc with detection limits of 0.5, 0.3 and 0.1 μg mL^{-1}, respectively. Immobilized *anti*-HBs antibodies on screen-printed carbon electrodes (SPCEs) for HBsAg detection and gave a LOD of 2.1 ng mL^{-1}. Hence, the electrochemical analysis was quantitative and more sensitive than the rapid testing. Paper based devices for HCV have also been developed incorporating the reverse-transcriptase step and subsequent amplification using LAMP to give a colorimetric readout as a strip/line from patient serum [81]. Given the ready availability of low cost anti-viral drugs, the need to be able to screen individuals who are asympomatic at the point-of-care or point-of-need is key. Patients who remain undiagnosed until irreversible clinical manifestations, such as liver cirrhosis and hepatocellular carcinoma, will otherwise continue to contribute to the 400,000 HCV related deaths reported every year.

The common symptoms of influenza include cough, sore throat, rhinitis, headache and fever. Influenza viruses include Influenza A viruses (IAVs), Influenza B viruses (IBVs) and Influenza C viruses (ICVs) [82]. PADs have attracted extensive attention in influenza diagnosis. Chromatographic analysis of influenza A nucleoprotein [83], colorimetric analysis of H1N1 antigen [84] and pH1N1 nucleoprotein [85], differential pulse voltammetry (DPV) analysis [86] and EIS analysis [87] of H1N1 virus have been demonstrated on PADs. Notably, Bhardwaj et al. [87] adopted a paper immunosensor based on vertical flow for electrochemical and colorimetric detection of H1N1 virus (Fig. 3b). After sample injection, the horseradish peroxidase labelled antibodies (HRP-Abs)-H1N1 complex was concentrated on the conjugate pad, thereby achieving rapid detection in only 6 min. The sandwich immune response of HRP-AbH1N1-Ab on the gold electrode was measured for EIS quantification. At the same time, a scanner was used to capture the color

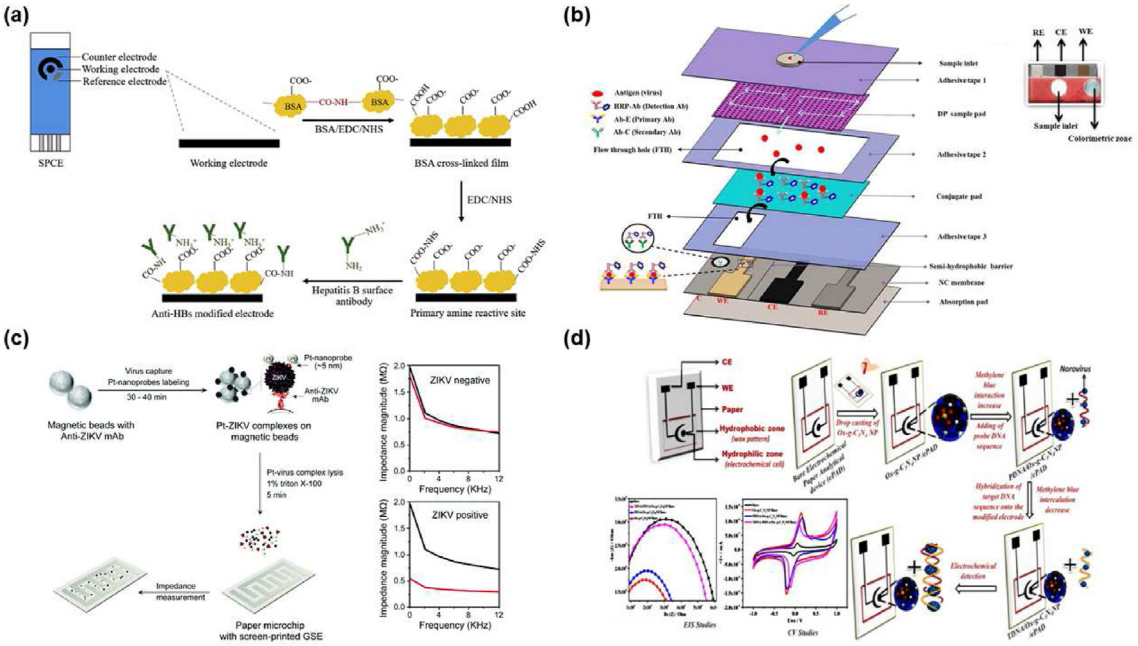

Fig. 3. Examples of PADs for infectious disease diagnosis, including (a) hepatitis, (b) influenza, (c) zika and (d) norovirus. (reprinted from Refs. [77,87,91,96] with permission from Elsevier and Royal Society of Chemistry).

signal of the free HRP-Abs. The detection limits obtained by EIS analysis and colorimetric analysis were 3.3 and 1.34 PFU mL^{-1}, respectively. The colorimetric method does not require any complicated equipment, but usually only provides semi-quantitative results. The EIS method can offer quantitative results and even detect low-concentration analytes that cannot be detected by the colorimetric method. The combined use of two methods can overcome the shortcomings related to the use of separate technologies, with double assurance to reduce false results.

Zika virus (ZIKV) is a mosquito-borne virus spread by *Aedes aegypti* in tropical and subtropical ecosystems [88]. ZIKV can be spread through body fluids, and common symptoms include rash, muscle pain, headache and mild fever. PADs made of Whatman Grade 1 Filter Paper, Whatman Grade 4 Cellulose Chromatography Paper and Whatman 3 MM Chromatography Paper have been applied for detecting *anti*-ZIKV-NS1 immunoglobulins [89], Zika RNA [90], and Zika virus [91,92], respectively. For example, a deployable bio-plasmonic paper-based device (BPD) was prepared to detect *anti*-ZIKV-NS1 immunoglobulins using localized surface plasmon resonance (LSPR) [89]. BPDs were validated for target detection in serum, indicating that BPDs provided a new strategy for effective target determination in the complex physiological environment. A paper microchip with SPEs based on viral lysate impedance spectroscopy and platinum nanoprobes was also presented to detect Zika virus, with a LOD of 10 copie μL^{-1} in plasma, urine and semen (Fig. 3c) [91]. The use of platinum nanoprobes for virus labeling can increase the conductivity of the generated virus lysate, thereby improving detection sensitivity and specificity.

Norovirus is the main cause of disease outbreaks caused by contaminated food and water, as well as one of the main causes of acute gastroenteritis. Norovirus is highly infectious, with an infectious dose as low as 10^2 copies mL^{-1}, affecting 685 million people worldwide each year. Mie scattering detection of norovirus capsid protein [93], colorimetric analysis of GII.4 Sydney norovirus RNA [94] and trigger RNA of GII.4 and GII.17 norovirus [95], EIS analysis of norovirus DNA [96], and fluorescence analysis of norovirus [97–99] have been achieved using PADs. In 2017, Cho et al. [93] developed a paper-based particle immunoagglutination assay for norovirus capsid protein detection, involving smartphone-based Mie scattering detection. By introducing three concentrations of *anti*-norovirus-conjugated particles into three channels of the wax-printed PAD, a linear response range covering 7 orders of magnitude and a LOD of 10 pg mL^{-1} were obtained. In 2020, Rana et al. [96] proposed an ePAD for norovirus DNA detection by incorporating oxidized graphitic carbon nitride (Ox-g-C_3N_4) (Fig. 3d), with a LOD of 100 fM within 5 s. Although Ox-g-C_3N_4 nanosheets can provide biocompatibility and enhance the sensing signal, the nanoparticles need to be further optimized to strengthen the stability response.

COVID-19 is an emerging infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which subsequently caused a global pandemic [100]. Compared with the total confirmed cases of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), the number of COVID-19 confirmed cases has increased by over 90 times [101]. Recently, PADs have been applied for detecting SARS-CoV-2 RNA using N-gene specific antisense oligonucleotides (ssDNA) capped AuNPs [102], SARS-CoV-2 spike glycoprotein using N-acetyl neuraminic acid based on its glycan-binding function [103], and SARS-CoV-2 humanized antibody using HRP conjugated antibody and the 3,3′,5,5′-tetramethylbenzidine (TMB) substrate [104]. In 2020, Zhu et al. [105] established a mRT-LAMP-LFB assay to detect ORF1ab and N genes, which employed a multiplex reverse transcription loop-mediated isothermal amplification (mRT-LAMP) coupled with a nanoparticle-based lateral flow biosensor (LFB) assay. The LFB consisted of a sample pad, a conjugate pad, a nitrocellulose membrane and an absorbent pad (Fig. 4a). The assay could be finished within 1 h, which included sample collection (3 min), RNA extraction (15 min), RT-LAMP reaction (40 min) and result indicating (<2 min). Although the sensitivity and specificity of the assay were both 100%, further research should be performed on more types of clinical samples. A paper-based microfluidic ELISA platform consisting of a pulling-force spinning top was also developed for SARS-CoV-2 receptor binding domain (RBD)-based IgA/IgM/IgG

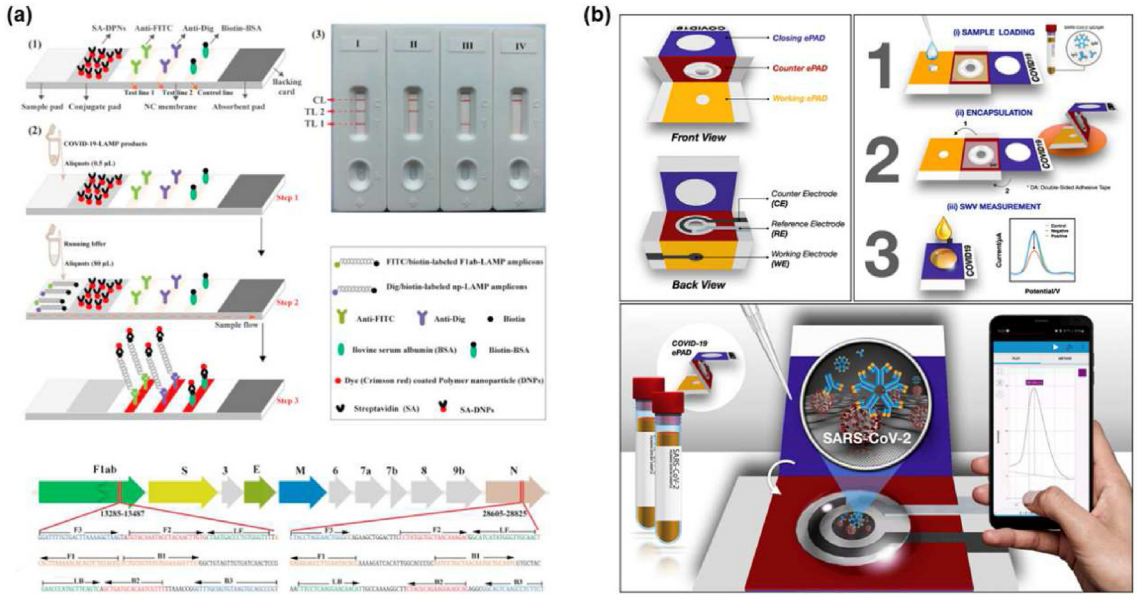

Fig. 4. Examples of PADs for COVID-19 diagnosis, including (a) a COVID-19 mRT-LAMP-LFB assay, and (b) a COVID-19 label-free paper-based electrochemical platform. (reprinted from Refs. [105,107] with permission from Elsevier).

quantification in human blood [106]. Apart from colorimetric analysis, electrochemical analysis has also been demonstrated on PADs for COVID-19 diagnosis. In 2021, a COVID-19 ePAD containing a working ePAD, a counter ePAD, and a closing ePAD was designed (Fig. 4b) [107]. The SARS-CoV-2 spike protein was immobilized on the working ePAD to capture antibodies. The immunocomplex formation between the antibodies and the spike protein would trigger the disruption of the redox conversion ($[Fe(CN)_6]^{3-/4-}$), which could be monitored by SWV technique. The detection limit of this device was 1 ng mL^{-1}, which was 3 orders of magnitude higher than the sensitivity of the colorimetric lateral flow assay (LFA).

3.2. Paper-based analytical devices for multiplexed detection of infectious diseases

The outbreaks of different infectious diseases have brought a serious human health crisis [108]. The number of biomarkers used for infectious diseases has increased accordingly, so it is important to develop methods for multiplexed detection of infectious diseases. In clinical diagnosis, multiplexed testing can reduce diagnosis time and expense, and ensure accurate and effective diagnosis [109]. Multiplexed real-time PCR, ELISA, microarrays and next-generation sequencing have been applied for infectious disease diagnosis [110]. However, these methods are usually time-consuming and cost-consuming. Therefore, an immediate necessity is the development of rapid, economical and reliable platforms for multiplexed detection of infectious diseases.

Recently, investigators have recognized the critical role played by PADs for multiplexed detection of infectious diseases. For example, a paper-based platform was tested for multiplexed electrochemical ELISA detection of HIV p24 and HCV antibodies for HIV and HCV diagnosis [111]. The platform included an electrochemical microfluidic paper immunosensor array (E-μPIA) and a handheld potentiostat, which could simultaneously detect 8 samples in 20 min and then transmit results to a portable electronic equipment for remote medical treatment through wireless communication function. A paper-based immunoassay was also adopted for multiplexed detection of malaria pLDH, malaria HRP2 and dengue NS1 type 2 to determine the fever cause [112]. The reagents for each immunoassay were spatially separated in the 3D paper-based structure, which made it possible to adjust the experimental conditions independently. It was demonstrated that the results of the multiplexed immunoassay were consistent with the single immunoassay. To improve the detection efficiency in on-site diagnosis, it is necessary to integrate the lysis function such as by treating paper layer with lysis solution. Moreover, a lateral flow chromatography assay was prepared for multiplexed detection of DENV NS1 protein, Yellow Fever Virus (YFV) NS1 protein, Ebola virus Zaire strain (ZEBOV) glycoprotein for the diagnosis of dengue, yellow fever and Ebola [113]. The optical properties of AgNPs could be employed for multiplexed detection of biomarkers through their adjustable absorption spectrum. Different sizes of AgNPs were combined with specific antibodies, and the colors of AgNPs were used to distinguish three pathogens.

In 2020, Batule et al. [114] presented a two-step paper-based system for extraction, amplification and detection of viral RNA for the diagnosis of zika, dengue and chikungunya. A lateral-flow paper strip was used to capture and elute viral RNA from serum in 5 min, and another paper chip was applied for RT-LAMP amplification and detection of viral RNA in 50 min (Fig. 5a). The system could complete the detection process in an hour, with a detection limit of 10 copies μL^{-1} in serum. However, the system still required two separate steps to extract and detect viral RNA. In 2020, the same group [115] developed a one-step paper-based integrated device for virus detection in human serum to diagnose zika, dengue and chikungunya. The paper chip was fabricated based on the combination of horizontal and vertical flow in a 3D stacked structure, which integrated RNA extraction, automatic flow control and RT-LAMP technology (Fig. 5b). Besides, the RT-LAMP dried reagents were immobilized in the corresponding area of the paper chip. After the serum sample was added, the target RNA was concentrated on the binding pad, and then transferred to the reaction pad for RT-LAMP reaction. The detection of three viruses in serum could be completed within 60 min at 65 °C, with a linear range of 5−5000 copies μL^{-1}. The use of PADs has also been extended to the multiplexed analysis of a range of infectious reproductive diseases in

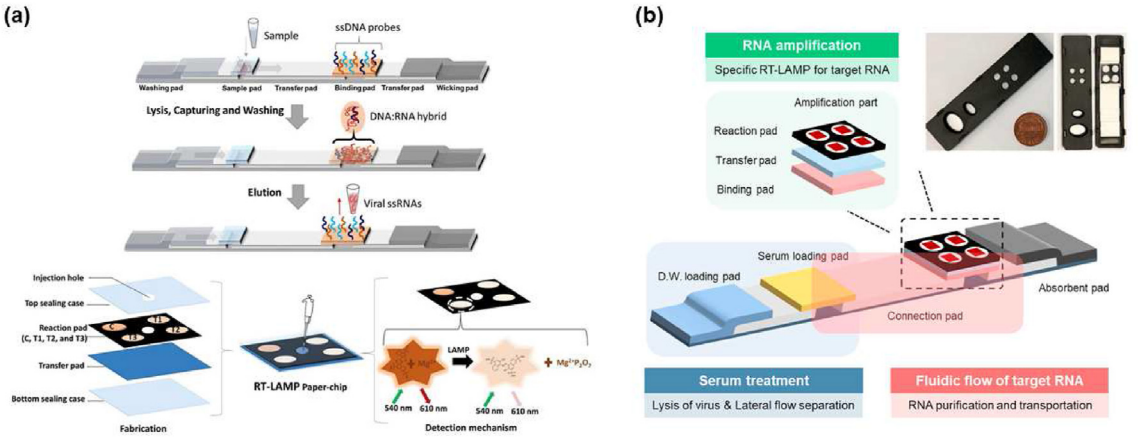

Fig. 5. Examples of PADs for multiplexed detection of infectious diseases, including zika, dengue and chikungunya (reprinted from Refs. [114,115] with permission from Elsevier).

livestock with measurements made at the "pen-side" in agricultural settings [116], using paper microfluic origami devices for sample preparation with a convenient field based measurement.

Using antibodies, synbodies, aptamers, probes, antigens or enzymes, PADs can be designed for infectious disease diagnosis. The development of PADs based on colorimetric, chromatographic, electrochemical, fluorescent, ECL ICA and SPR analysis combined with signal amplification strategies is of great significance for the rapid and reliable diagnosis of infectious diseases. Given the increase in the number of infectious diseases, there is an urgent need to develop multiplexed PADs combining multiple biosensing technologies to analyze clinical samples, including blood, plasma, serum, saliva, urine, faeces, semen, cell lysates and infected tissue.

3.3. *Paper-based analytical devices for point-of-care testing*

With the widespread of numerous diseases, there is an urgent need to develop PADs into integrated devices for POC use. Biotechnology, nanotechnology and biosensing, microfluidic, and electronic technologies are attractive to be implemented in POC devices. It is significant to integrate sample collection, separation, nucleic acid extraction, amplification, and detection into an automatic platform. The integrated PADs can be employed for vital signs detection, disease diagnosis and environmental monitoring, which establishes new avenues for the development of POC applications. In resource-poor settings lacking healthcare facilities, POC PADs are affordable alternatives for disease diagnosis. PADs have been developed to measure biomarkers, diagnose disease infectivity and identify antibiotic resistance. For example, companies such as "Diagnostics for All" and "Intellectual Ventures" are developing PADs for diagnosing dengue, HIV, hepatitis, malaria, TB and other diseases. Due to the variety of target analytes, it is imperative to select appropriate biorecognition elements for each analyte. Biorecognition elements (e.g., enzymes, aptamers, and antibodies) can be immobilized on paper substrates and dried by a variety of methods (e.g., physical, chemical, biochemical conjugation, and bioactive pigments), which is especially suitable for storage and use in remote areas.

Accurate detection of target analytes depends not only on the affinity of the biorecognition element but also on the effectiveness of the detection method. Colorimetric assays are widely used for POC PADs and provide "yes/no" results. The results can be obtained by visual inspection or equipment record. However, the results of visual inspection may be affected by factors such as environmental lighting, viewing angle, color intensity and uniformity. Thinner paper substrates will promote faster reagent flow and better color readings. Although colorimetric assays are easy to implement, they require complementary analytical instruments for quantitative analysis. Electrochemical detection, on the other hand, does not require a light source and can provide "digital" quantitative results. With the advantages of portability, selectivity, and sensitivity, POC detection can be achieved using ePADs, electrochemical workstations, and smartphone applications. In general, detection methods (e.g., electrochemistry, fluorescence, and SPR) may require expensive and sophisticated equipment (e.g., electrochemical workstations, fluorescence detectors, and SPR instruments) to accurately interpret results.

The LFA is one of the most common POC PADs, typically comprising a sample pad, a binding pad, an absorbent pad, a test line, and a control line. The sample added to the sample pad is wicked through the device, interacting with the labeled conjugated antibody and the immobilized capture antibody. When the target analyte is present in the sample, a colored band forms on the device because the labeled antibody is retained by the capture antibody. While LFAs are simple, affordable, and specific, they can only provide qualitative results and relatively poor detection limits compared to laboratory-based assays. For example, Tang et al. [117] adopted an integrated PAD for *S. typhimurium* detection, which consisted of nucleic acid extraction, thermophilic helicase-dependent amplification (tHDA) and LFA detection (Fig. 6b). After tHDA, the copper sheets were moved to the detection area, followed by the addition of the extracted DNA and running buffer to the LFA device. The detection limits in milk, juice, eggs and wastewater were 10^2–10^3 CFU ml^{-1}, indicating that it could become a powerful tool for detecting food contamination and environmental pollution. A LFA device was also prepared for HIV detection by integrating the dialysis method into the device (Fig. 6c) [118]. The authors integrated the hygroscopic polyethylene glycol (PEG) buffer, glass fiber and semi-permeable membrane into the 3D printed LFA device to achieve sample concentration and detection. Furthermore, Phillips et al. [62] presented a microfluidic rapid and autonomous analysis device (microRAAD) for lateral flow immunoassay (LFIA) of HIV RNA in blood (Fig. 6d). The pre-dried RT-LAMP reagents were first immobilized on the PAD, then the PAD was assembled into a plastic housing with a temperature control circuit for resistive heating. The detection limit was 100 copies of HIV-1 RNA, which highlighted its great promise for on-site HIV diagnosis through combining molecular, capillary flow control and heating control technologies.

With the development of electronic technology and wireless technology, the combined applications of smartphones and POC

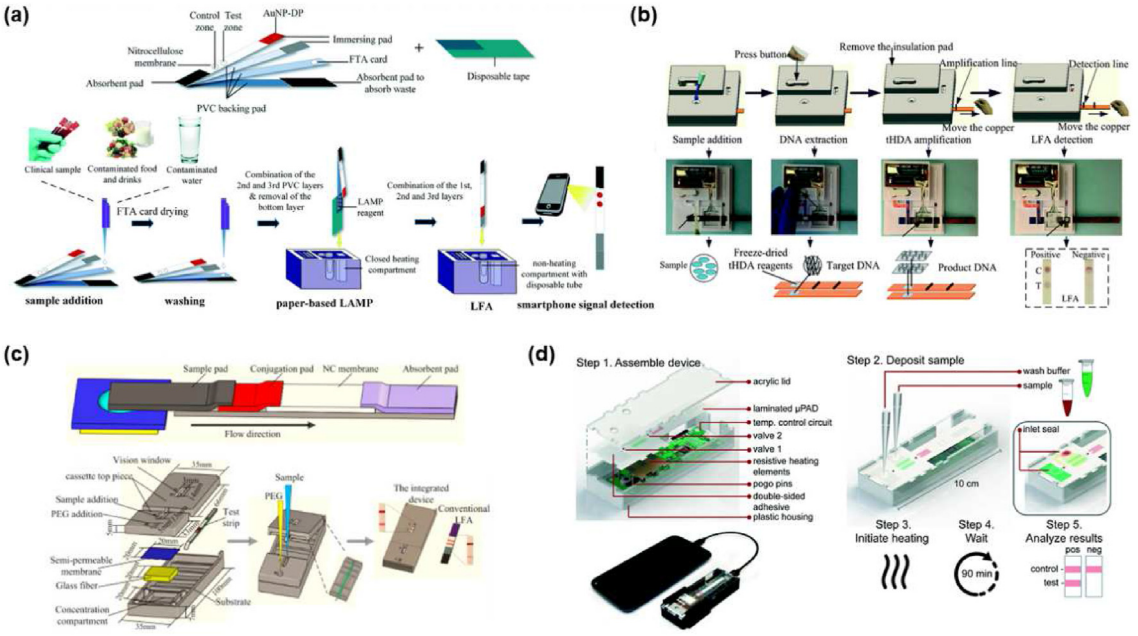

Fig. 6. Examples of PADs for POC use. (a) An integrated paper-based biosensor for *E.coli* testing. (b) An integrated paper-based device for *S. typhimurium* detection. (c) A LFA device for detecting HIV nucleic acid. (d) A microRAAD for LFIA detection of HIV RNA. (reprinted from Refs. [62,117–119] with permission from Royal Society of Chemistry and Elsevier).

PADs have attracted great interests. Smartphones possess lightweight form factors, high-resolution digital cameras and multiple computing applications, so they are suitable for acquisition, processing, analysis, and transmission of detection results from PADs in resource-constrained environments. In addition, smartphones can address the non-homogeneity issues associated with paper substrates, which is beneficial for the detection of complex analytes [56]. By using white LEDs, smartphones can maintain constant lighting conditions and also average the light signal generated by the non-homogeneous cellulose fibers. For instance, Choi et al. [119] tested an integrated paper-based biosensor for nucleic acid testing. In Fig. 6a, the Fast Technology Analysis (FTA) card and glass fiber were integrated into a lateral flow strip for sample addition, washing, paper-based LAMP, eye detection or smartphone quantification. A handheld battery-powered heating device was used for on-site LAMP tests. Detection limits of 10–1000 CFU mL^{-1} were measured for *E.coli* in spiked drinking water, milk, blood and spinach. More recently, Guo et al. [56] developed a smartphone-based end-to-end platform for multiplexed DNA-based lateral flow diagnostic assays of malaria in rural Uganda. Notably, their approach, combined with deep learning algorithms for local decision support and blockchain technology for secure data management, created the possibility of integrating infectious disease data within a surveillance framework.

Against the background of the severe COVID-19 epidemic, POC PADs are attractive to be implemented in efficient and reliable COVID-19 diagnosis. Biotechnology, nanotechnology, biosensing, microfluidic and electronic technologies facilitate the design of POC PADs. As mentioned above, POC PADs have been used to analyze biomarkers for disease diagnosis. With the advantages of cheapness, portability, easy operation, high sensitivity/specificity and low sample/reagent consumption due to their miniaturized and integrated components, POC PADs meet the World Health Organization guidelines "REASSURED" [26].

However, the development of fully automated POC PADs for on-site pandemic monitoring in clinical and environmental samples remains challenging. Further research should be conducted to improve sensitivity and specificity, enhance stability and efficiency, and reduce analysis time. Furthermore, multiplexed biosensing systems can further increase analytical capabilities, providing a low-cost, portable and user-friendly diagnostic platform for resource-constrained areas.

4. Paper-based analytical devices for wastewater surveillance

With the rapid development of society, numerous different types of wastewater have been produced, including surface runoff from urban areas, wastewater from agriculture, industry, and households [120]. Wastewater is an ideal living medium for pathogenic organisms, and these pathogenic organisms pose a major threat to human health. Human pathogens in wastewater mainly include bacteria and viruses. Human excreta in domestic sewage is the source of most human pathogens in wastewater. For example, enteric pathogens enter wastewater from human feces and urine. In addition, wastewater from animal breeding, gathering and processing industries also have harmful effects on human health because livestock and poultry can be infected with zoonotic enteric pathogens. Wastewater-based epidemiology (WBE) has been used to identify a variety of biomarkers, including illicit drugs, pharmaceutical and personal care products, population-scale markers, industrial chemicals and biological agents [121]. WBE-based PADs have shown significant potential for the detection of pathogenic organisms in wastewater.

Bacteria are the most diverse human pathogens in wastewater. The main human bacterial pathogens in wastewater include *Escherichia*, *Salmonella*, *Shigella*, *Leptospira* and *Vibrio*. Moreover, the overuse of antibiotics may cause water pollution, and accelerate the rapid emergence of antibiotic resistance genes (ARGs) and bacteria (ARB) in wastewater [122]. The resistant organisms may enter human bodies by diet directly or by food chain indirectly and bring a serious health risk to humans. A low-cost PAD was proposed for colorimetric detection of the bacteria resistant to β-lactam antibiotics in sewage and the resistance of certain bacteria in environmental waters [30]. The hydrolysis of the β-lactam ring

mediated by β-lactamase caused the color to change from yellow to red. The PAD showed sensitivity similar to that of a microplate reader or a microtiter plate at a lower cost (USD 0.20). Although this method reduced the detection time by 14–20 h, it remains challenging to integrate the test into a ready-to-use module.

Electrochemical PADs for the detection of sewage bacteria have also been designed. While colorimetric PADs can provide a simple visual analysis method, electrochemical detection is not limited by background sample coloring and can provide lower detection limits and easily quantifiable results using a hand-held electrochemical workstation. By screen printing carbon electrodes onto hydrophobic paper, Rengaraj et al. [123] reported functionalized SPCEs for the detection of sludge bacteria. The hydrophobicity of the Fabriano 5 HP paper contributed to electrode functionalization and prevented non-specific adsorption of solutions during electrode preparation. The SPCE surface was first functionalized with carboxyl groups, and Concanavalin A was then covalently immobilized as a bioreceptor for EIS measurement of bacteria in water. The system showed a linear range of 10^3–10^6 CFU mL^{-1} with a LOD of 1.9×10^3 CFU mL^{-1}. Future work will focus on the use of nanomaterials to increase the surface area of the SPCE, thereby achieving a lower detection limit close to the threshold concentration of *E. coli* in water.

In 2014, Bisha et al. [124,125] adopted a paper-based platform for the detection of *E.* coli, *Salmonella* and L. *monocytogenes* in food and water. Later, they improved the bacteria detection platform and introduced a comparison between colorimetric detection and electrochemical detection. In 2017, the same group [33] prepared a novel platform for dual electrochemical and colorimetric detection of fecal indicator bacteria (FIB) in surface irrigation water and food (Fig. 6b). SWV analysis was based on the use of stencil-printed carbon electrodes on transparent film, while colorimetric analysis was based on cardboard box and smart phone for real-time monitoring. *E. coli* produced β-galactosidase and β-glucuronidase, while *Enterococcus* species produced β-glucosidase. These enzymatic reactions could be used as indicators for FIB analysis, and FIB detection could be performed using specific substrates. The combination of two methods could overcome the shortcomings of individual techniques, which was more suitable for effective detection of a wider range of bacterium types. Although the detection time of two methods was similar, the detection limit of electrochemical detection was lower than that of colorimetric detection. The possibilities remain to be explored to improve sensitivity, such as employing inducers to enhance enzyme activity or adding electrochemical and chemical pre-concentration steps.

Viruses are another type of human pathogens in wastewater. The main viruses in wastewater contain enteroviruses, including norovirus, adenovirus and astrovirus [120]. Besides, industrial waste from slaughterhouses can introduce zoonotic viruses into wastewater. Human viruses are generally excreted with the feces and urine of infected people and spread through the urban or rural water cycle [126]. These viruses may survive for a long time in wastewater and surface water. For example, avian influenza viruses and some coronaviruses are comparatively stable in water, and occasionally spread to humans causing disease outbreaks.

Human viruses have been detected in wastewater over the past decades, suggesting that WBE has great potential for early identification of viral outbreaks through regular monitoring of virus concentrations and diversity in wastewater. In general, WBE can provide information on virus population size and assess spatial and temporal trends in virus occurrence in watersheds [127]. Common techniques including virus isolation, immunofluorescence, ELISA and nucleic acid amplification techniques have been applied for virus detection. Generally, many human enteroviruses in municipal wastewater have been quantified by quantitative reverse transcription polymerase chain reaction (RT-qPCR), with a concentration of up to 10^9 copies per liter. Although these methods are reliable, they are time-consuming and labor-intensive. PADs hold great potential for analyzing viruses in complex organic matrices extracted from surface water ecosystems and wastewater-related samples.

Fluorescence analysis of HIV-1 p24 antigen was determined by a carbon dot-based paper immunoassay (CDPIA) using carbon dots prepared by citric acid and ethylenediamine through hydrothermal method [61]. The sandwich immunoassays for HIV-1 p24 antigen determination were performed on Whatman filter paper and nitrocellulose paper. Compared with CDPIA on Whatman filter paper, the sensitivity of CDPIA on nitrocellulose paper was four times higher and the analysis time was three times shorter. In another study, fluorescent detection of norovirus was demonstrated by a wax-printed PAD with aggregated antibody-conjugated submicron particles [98]. The authors further developed an image analysis algorithm to separate only the aggregated particles, so the generated measurement results were not influenced by illumination deviations and interference. The detection limits for norovirus detection were 1 copy μL^{-1} in deionized water and 10 copies μL^{-1} in reclaimed wastewater, respectively. Therefore, a combination of PAD, smartphone-based fluorescence microscope and mobile applications establishes new avenues for quantifying complete norovirus in various environmental water samples.

In 2021, a PAD integrated with a reduced graphene oxide hybrid multi-walled carbon nanotube nanocircuit heater integrated (HiPAD) was applied to a colour LAMP assay for SARS-CoV-2 detection [128]. The successful use of reduced graphene oxide/multi-walled carbon nanotubes (rGO/MWCNTs) as an electrothermal module solved a major field challenge by miniaturizing and integrating a portable heater. Interestingly, a slidable paper device integrated with dopamine polymerization was also developed for LAMP amplification of SARS-CoV-2 [129]. Dopamine-based DNA detection achieved clear readings based on dispersed and aggregated polydopamine, corresponding to the presence and absence of pathogens. In addition, highly conductive graphene/carbon ink was screen printed as a working electrode and immobilized with IgG antibodies for EIS analysis of SARS-CoV-2 spike protein [130]. The EIS detection of SARS-CoV-2 spike protein antibody was also realized on μPADs with directly synthesized zinc oxide nanowires (ZnO NWs) [131]. In this way, the performance of paper-based biosensors was improved, which highlighted the extraordinary ability of nanomaterials to provide superior EIS biosensing performance.

Conventional studies for virus detection are usually performed on individuals in clinical settings following viral outbreaks. In the context of the COVID-19 outbreak, RT-qPCR is the routine method for SARS-CoV-2 detection. As an alternative to RT-qPCR, PADs can provide rapid and accurate test results without requiring laboratory-based instruments or specialized technicians. Furthermore, WBE is a complementary disease surveillance system and an early warning tool for viral outbreaks at the community and population levels [132]. Wastewater analysis can obtain infection status in a specific area, which is conducive to early warning of infectious diseases. Portable paper-based analytical tools meet WBE requirements and can therefore be used to detect pathogenic organisms in wastewater. By regularly monitoring the concentration and diversity of pathogenic organisms in wastewater, combined with monitoring biomarkers for population adjustment, the onset of disease outbreaks can be detected early [133]. Besides, carefully designed wastewater sampling locations will allow determination of critical locations for the onset of disease outbreaks. Other factors such as viral shedding rates and environmental degradation rates must also be considered to accurately estimate disease cases. Within this viewpoint, the combination of PADs and WBE provides

new insights for low-cost and rapid detection of pathogenic organisms to monitor disease transmission for prevention, intervention and control.

5. Conclusions and perspectives

PADs offer excellent opportunities for effective analysis in various fields such as medical diagnosis, environmental and agricultural analysis, food safety as well as more recently WBE. Generally they are cheap, portable, sensitive, specific, user-friendly, energy efficient and require only one analyte less and support multiplexed analysis [134]. The most frequently used wax printing method is not only easy to use but also quite affordable and suitable for scale-up production. In contrast to electrochemical and luminescent methods, colorimetric methods do not require special accessories such as voltage regulators and excitation light sources, simplifying the conditions of use. Compared with traditional microfluidic devices, PADs transport fluids by wicking and capillary action, which avoids the need for pumps. PADs also reduce the consumption of materials, samples, reagents, and wastes, and require less laboratory equipment and specialized technicians. In addition, electronic devices can be further used in conjunction with PADs as cost-effective, accurate, and field-portable analytical devices. Therefore, PADs meet the requirements of green analytical chemistry and sustainable development [135].

In this paper, we introduced the applications of the latest PADs in infectious disease diagnosis. Although various PAD platforms have been applied for infectious disease diagnosis, many challenges still need to be overcome [13,16,136]. The paper substrate properties, fabrication techniques, and detection methods generally limit their applications. Sample evaporation during sample transport within the device fluidic channels may reduce the transport efficiency of the sample. The hydrophobic agent may not create hydrophobic barriers strong enough to withstand samples with low surface tension. Structural differences in paper fibers may reduce the accuracy of the hydrophobic barriers and the rate of fluid wicking, thereby affecting the detection results. Essential biological reagents (e.g., enzymes, aptamers, and antibodies) may be denatured by harsh environmental conditions during shipping and storage. Additionally, false positives and false negatives may occur due to cross-reactivity or low concentrations.

An ideal PAD platform for infectious disease diagnosis should meet the requirements of WHO REASSURED framework. However, it is usually difficult to achieve these goals. Although, most PADs exhibit excellent analytical performance in the pristine and spiked samples, they cannot obtain effective detection results in clinical samples due to the inevitable troublesome matrix effects. Besides, few PADs are used to conduct large-scale clinical trials to evaluate their practicality, which may be due to the lack of clinical samples involving pathogen infections [19]. Therefore, the sensitivity, specificity, reproducibility, assay time and detection range of PADs must be improved by detecting sufficient clinical samples. To meet the requirements of high-throughput analysis of infectious diseases, it is critical to develop multiplexed PAD platforms for identifying multiple pathogens in clinical diagnosis.

PADs can not only become a key technology for infectious disease research, but also can monitor pathogenic organisms in wastewater. Most of the reported PADs are only used for the analysis of drinking water and surface water samples, and only a small number of PADs are used for wastewater analysis. For wastewater analysis, the biorecognition molecules may interact with the matrix compounds of samples and produce non-specific interference signals on the transducers, resulting in the low sensitivity and selectivity of PADs. The biorecognition molecules may also lack long-term stability at room temperature, thereby reducing the stability and reproducibility of PADs [127]. As stated earlier, population health information in wastewater can be obtained through high-frequency sampling and analysis with different temporal and spatial resolutions. However, information on excretion biomarkers, sewer stability, and population catchment size is needed to convert human biomarker concentrations into standardized population load and drug consumption after PAD analysis of wastewater [137]. In the context of COVID-19, there is also a significant opportunity to use WBE-based PADs to investigate re-emergence of viral outbreaks in communities. The comprehensive development and application of this new epidemiological technique further facilitates the study, identification and prediction of other disease outbreaks. Specifically, methods for the concentration, extraction, purification and detection of pathogenic organisms from wastewater need to be optimized. Quantitative risk assessment of organisms in wastewater and investigation of organism survival in wastewater are also required.

With the increasing incidence of infectious, food and waterborne diseases, there is a growing interest in PADs for POC applications for diagnosis across community settings. Recent advances in PADs have made it possible to achieve cost-effective testing in resource-limited environments. Various PADs are being developed to extract nucleic acids from a variety of biological samples, such as commercial filter papers, nucleic acid filtration separation methods and paper-fold-based extraction. Some studies have also used water baths or small heaters to provide reaction temperatures. The ideal POC PAD should integrate sample preparation, nucleic acid extraction, amplification and detection into a fully automated and portable paper-based device. Further effort is required to develop economical, stable, reproducible, multiplex, automated, portable and user-friendly PAD platforms for POC diagnosis and wastewater surveillance at low-resource settings [56]. For example, by combining WBE, biotechnology, nanotechnology, biosensing, pathology, microfluidics and electronics, PADs can provide cost-effective, portable and user-friendly detection of SARS-CoV-2 in wastewater and provide early warning of pandemics [138]. Some PADs have been developed into integrated devices, but the commercialization of PADs is still in its infancy. There is a need to reduce production costs, simplify manufacturing procedures and improve production efficiency before PADs can be commercialized on a large scale [139].

In the future, artificial intelligence (AI), big data analytics (BDA) and Internet of Things (IoT) can be combined with PADs for POC diagnosis and wastewater surveillance [56]. AI devices can perform multi-step analysis to predict disease profiles using various algorithms [140]. For example, Metabiota has used an epidemic prediction tool to warn of coronavirus outbreaks before they were officially declared in Japan and South Korea [141]. Medical imaging-based AI systems have also been used for the diagnosis, prediction and drug/vaccine development [142]. In terms of BDA, public health big data, which often includes patient information collected from large volumes of electronic health records, will help to enhance disease surveillance and show great potential for infectious disease modelling and prediction [143]. IoT technologies including wearable devices, drones and smartphone apps will also be used for early diagnosis, patient monitoring and protocol implementation [144]. In addition to POC diagnosis, AI and BDA will be applied to the digitization of the wastewater industry to realize new functions of wastewater monitoring. A novel framework using WBE and AI technologies was proposed to help decision makers detect and predict future virus outbreaks [141]. To develop commercially available PADs for smart POC diagnosis and wastewater surveillance, academic researchers, medical professionals, industrial engineers and government agencies should work together to explore and improve the biometric elements, statistical analysis and hardware design of PADs.

Author statement

Yuwei Pan: Conceptualization, Writing - original draft, Writing - review & editing., **Kang Mao, Qinxin Hui, Baojun Wang and Jonathan Cooper:** Writing - review & editing, **Zhugen Yang:** Conceptualization, Writing - original draft, Writing - review & editing, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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