Biosensors and Bioelectronics 163 (2020) 112291

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: http://www.elsevier.com/locate/bios

Advanced "lab-on-a-chip" to detect viruses – Current challenges and future perspectives

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ARTICLE INFO

Keywords:
Virus outbreak
Microfluidic chip
Lab on a chip
Virus detection

ABSTRACT

Massive viral outbreaks draw attention to viruses that have not been thoroughly studied or understood. In recent decades, microfluidic chips, known as "lab-on-a-chip", appears as a promising tool for the detection of viruses. Here, we review the development of microfluidic chips that could be used in response to viral detection, specifically for viruses involved in more recent outbreaks. The advantages as well as the disadvantages of microfluidic systems are discussed and analyzed. We also propose ideas for future development of these microfluidic chips and we expect this advanced technology to be used in the future for viral outbreaks.

1. Introduction

Viruses infect millions of individuals each year resulting in serious morbidity (Hutchinson, 2018), birth defects (Rasmussen et al., 2016), and mortality (Campos et al., 2015). Viruses have the ability to rapidly evolve and transmit through multiple modes such as the respiratory tract (Mazur et al., 2015; Young et al., 2015), digestive tract (Ferrari et al., 2017) and skin (Hamel et al., 2015). Despite many discoveries related to the understanding of different aspects in virology, viruses are still a major cause of disease (Suratanee et al., 2010). In recent years, life-threatening viruses such as COVID-19 (Corman et al., 2020; Lorusso et al., 2020), Zika virus (ZIKV) (He et al., 2017; Petersen et al., 2016) and Ebola virus (EBOV) (Baize et al., 2014; Gire et al., 2014) have unexpectedly emerged and were difficult to tackle since there were no approved vaccines or effective treatments for the treatment of these viruses. In general, viruses cause significant economic burden to society and most are recognized as a public health emergency of international concern (PHEIC) by the World Health Organization (WHO) (Gostin et al., 2014; Gulland, 2016; Patel and Jernigan, 2020).

Traditional methods used for virus detection mainly involve cell culture (Hematian et al., 2016; Leland and Ginocchio, 2007), nucleic acids (Dominguez et al., 2018; Payungporn et al., 2006) and antigen-antibodies (Liao et al., 2009; Senthilkumaran et al., 2017). These methods, especially for nucleic acid detection methods, require expensive equipment and well-trained operators (Eivazzadeh-Keihan et al., 2019; Yeh et al., 2020). Moreover, these methods are unable to meet the needs of clinical diagnosis as well as provide timely details necessary for large viral outbreaks. Point of care (POC) enables simple, fast, autonomous and sensitive virus detection (Gervais et al., 2011; Gubala et al., 2012; Kumar et al., 2019; Yetisen et al., 2013). The POC device is currently available in the market (Chin et al., 2012), which is expected to reach USD 52.6 BN by 2025 and will experience a robust compound annual growth rate of 9.75% from 2019 to 2026. In response to viral outbreaks, advanced POC diagnostic technology must be equipped for both the home and clinical use.

Microfluidic chips, or "Lab on a chip", are versatile and promising technology (Bruijns et al., 2016; Koo et al., 2017; Li et al., 2017; Medlin and Orozco, 2017; Tangchaikeeree et al., 2017) that have the ability to integrate sample preparation, reactions and detection on a micron-scale chip (Basha et al., 2017; Kim et al., 2009; Kovarik et al., 2013; Toren et al., 2016). This advanced technology has both integrated and miniaturized characteristics, which can integrate a traditional laboratory

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https://doi.org/10.1016/j.bios.2020.112291
Received 16 March 2020; Received in revised form 2 May 2020; Accepted 10 May 2020
Available online 12 May 2020
0956-5663/

into a small chip. It uses a small amount of detection reagents and samples to obtain accurate test results in a short period of time, which is especially suitable for POC. Recently, dramatic paper-based microfluidics (Ahn et al., 2018; Reboud et al., 2019), centrifugal chips (Lee et al., 2006; Li et al., 2019a), wearable microfluidic devices (Gao et al., 2017; Koh et al., 2016; Nyein et al., 2018), digital nucleic acid detection chips (Song et al., 2018; Zhu et al., 2014) and others have been proposed for pathogen detection (Tsougeni et al., 2019) as well as disease screenings (Shuler, 2019) and additional applications (Yin et al., 2019). These microfluidic technologies have been systematically classified and summarized by lots of reviews (Bruijns et al., 2016; Kim et al., 2009; Koo et al., 2017; Kumar et al., 2019; Reinholt and Baeumner, 2014) to promote technological innovation of microfluidic systems.

This technology is also well-suited in Point of Care Testing (POCT) in viral detection (Yen et al., 2015). After many efforts, microfluidic technology provides a breakthrough in viral detection, leading it possible to efficiently detect viruses that threaten human health. As shown in Fig. 1, the microfluidics system can be used to detect the viruses both for clinical use and personal use. In addition, in response to virus detection, it is also necessary to have a full understanding of the virus including its subtypes, genotypes and other notable characteristics. In this review, we summarize viruses that have been of concern over recent years (Fig. 2) and discuss the application and performance of microfluidics for their detection. Moreover, we summarize the current shortcomings of microfluidics in viral detection and pave ideas for future development. We aim to promote technological innovations of microfluidic chips so they exert maximal effects for future virus outbreaks.

2. Microfluidic chips for virus outbreaks

2.1. Ebola virus (EBOV)

EBOV is an enveloped, negative-stranded RNA virus (de La Vega et al., 2015; de Wit et al., 2011) that belongs to the filoviridae family. It is known as the Ebola Virus Disease (EVD) and has a high mortality (Broadhurst et al., 2016). EBOV causes damage to blood vessels, the liver, spleen, kidney and immune system (Malvy et al., 2019). EVD symptoms such as fever, muscle pain, vomiting, and diarrhea can occur within 2–21 days after a person is infected with EBOV (Martines et al., 2015; Richards et al., 2018). The EVD is mainly prominent in West Africa, where the major 2014 outbreak infected a total of 28,646 people and led to the death of 11,323 individuals (Kinsman et al., 2017). This outbreak was the largest EVD epidemic since the discovery of EBOV in 1976 (Wang et al., 2016). During the outbreak, quantitative reverse transcription polymerase chain reaction (qRT-PCR), the gold standard method, was used to detect the virus (Broadhurst et al., 2016), but was found to be time-consuming as well as expensive (Kaushik et al., 2016; Pinsky et al., 2015).

Recently, microfluidics represents a promising technology for the detection of EBOV. One study (Magro et al., 2017) reported a paper microfluidic chip based on reverse transcription recombinase polymerase amplification (RT-RPA). This paper chip has both a positive and negative control area and can detect EBOV in 30 min. Moreover, results from 43 patient samples in Guinea showed that this paper chip has a 90% sensitivity compared to RT-PCR. Du et al., (2017b) proposed a microfluidic platform to extract and capture EBOV RNA using a photocleavable capture probe. This chip has the ability to perform 80 assays in parallel and its analytical method contains a LOD of 800 aM. Qin et al., (2019) proposed an automated and multiplexing system to detect EBOV RNA (Fig. 3 A). This system can complete 24 assays while using use Cas13a to generate fluorescent reporter RNAs resulting in a LOD of 20 pfu/mL from 10 μL EBOV RNA within 5 min.

There are five types of EBOV including the Bundibugyo Ebola virus (BDBV), Reston virus (RESTV), Zaire Ebola virus (ZEBOV), Tai Forest Ebola virus (TAFV) and Sudan Ebola virus (SUDV) (Taniguchi et al., 2012). Four (EBOV, SUDV, BDBV, TAFV) of the five subtypes are extremely severe and detrimental to humans (Khan et al., 2015). It is necessary to study microfluidic system capabilities for the detection of various EBOV types. Magro et al. also developed a multiplex paper chip to detect three types of EBOV based on RPA (Magro et al., 2017) (Fig. 3 B). Piraino et al., (2016) developed a microfluidic chip that combined digital and analog technologies. This chip contains a high dynamic range and can simultaneously detect three types of EBOV with a LOD of 1pM from 5 μL of serum. Brangel et al. (Brangel et al., 2018) reported a paper and smartphone-based platform to detect IgG antibodies against the virus in sera. Detection results testing 90 survivors and 31 uninfected individuals revealed 100% sensitivity (Fig. 3 C). Moreover, this platform was able to detect three types of EBOV. More recently, Lin et al. (Lin

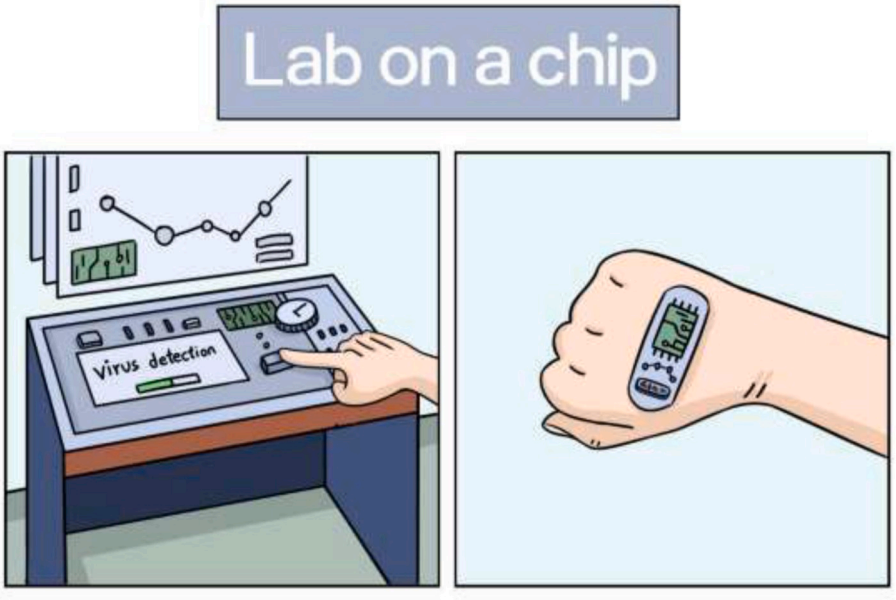

Fig. 1. Advanced microfluidics chip for efficient detection of viruses. Lab on a chip technology integrate various miniaturized laboratory functions on a single chip for the completion of steps in the traditional laboratory. The cooperation between clinical lab and individual users is crucial when faced the virus outbreaks. The microfluidics chip can be equipped for both the clinical and home use. It can be regarded as one of the most promising solutions in response to viral outbreaks.

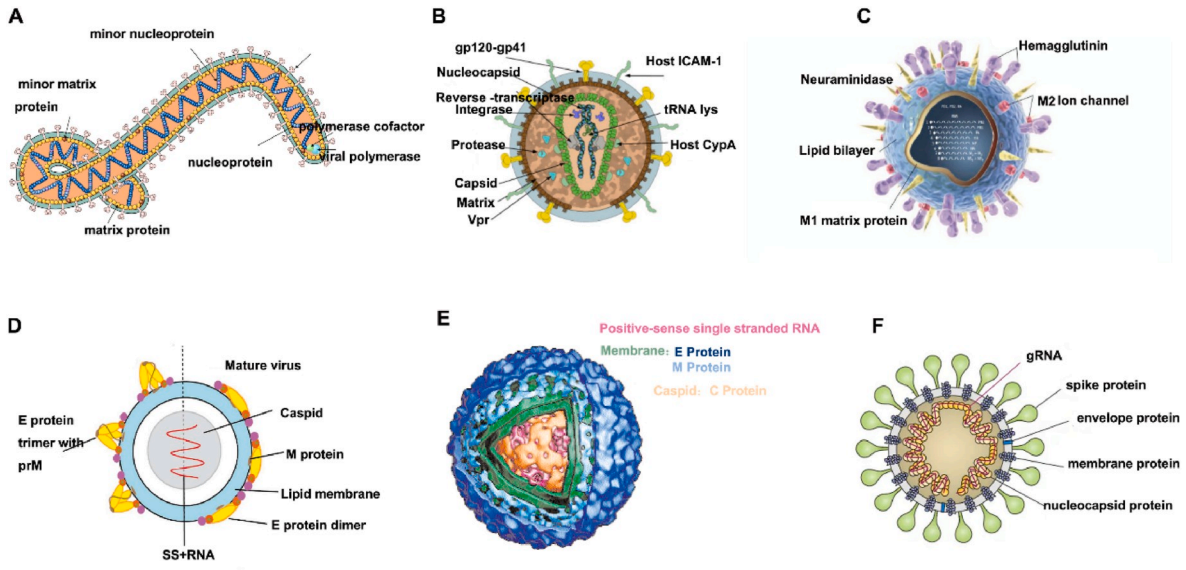

Fig. 2. Schematic representation of the structure of representative viruses. A: Ebola virus de (de Wit et al., 2011); B:Human immunodeficiency virus (Druce et al., 2016); C:Influenza virus (Kaiser, 2006); D:Zika virus (Qadir et al., 2018); E:Dengue virus (Zonetti et al., 2018); F:SARS-CoV-2 (Kim et al., 2020).

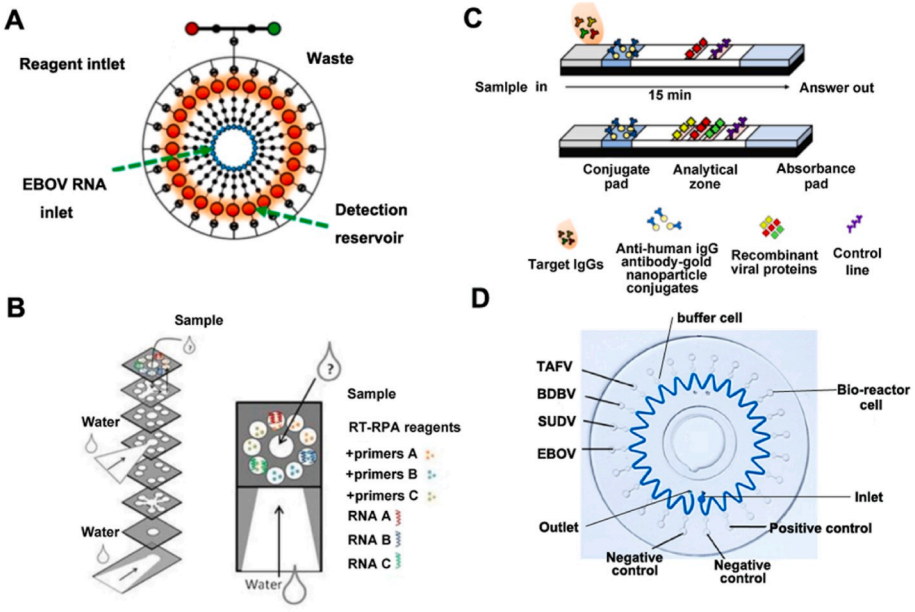

Fig. 3. Microfluidic system to detect EBOV. A: Microfluidic chips proposed by Qin et al., in 2018. This chip can detect 24 samples and contains pneumatic and fluidic layers. RNA was pumped into the chip and reacts with Cas13a−crRNA in the detection reservoir. Adapted from ref. 62 with permission from ACS Publications. B: Schematic of multiplexed paper-based microfluidic chips (Magro et al., 2017) Enlarged view and top view. This multilayered paper device contains 8 layers and 9-outlets. The detection method is based on RPA. RT-RPA reagents and three different primers for detection are freeze-dried in the chip. Adapted from ref. 60 with permission from Nature Publications. C: Paper chip proposed by Brangel et al. Serum forms complexes between the labeled gold nanoparticles (AuNPs) and the target analytes. Targeted IgG serum antibodies against single or multiple recombinant Ebola viral proteins bind to preprinted test lines, forming a visual red-purple line. A control line is used to validate assay function for the detection of antihuman antibody-gold nanoparticle conjugates. Results can be obtained in 15 min. Adapted from ref. 66 with permission from Nature Publications. D: Schematic of the microfluidic chip for detection of four EBOV species (Lin et al., 2019). Sample was placed into the chip through centrifugation. Primers were embedded into the chip and the amplified products were detected by a fluorescent marker. Adapted from ref. 67 with permission from Nature Publications. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

et al., 2019) developed a disc chip to detect the four EBOVs using the reverse transcription loop-mediated isothermal amplification (RT-LAMP) method (Fig. 3 D). The LOD of this system is 1 copy/μL for SUDV, 100 copies/μL for EBOV, 1000 copies/μL for BDBV and 10 copies/μL for TAFV detected in 50 min.

State-of-the art microfluidic detection systems can achieve cost-effective, quick (reported at 5 min) and accurate (as low as 1 copy) detection for EBOV at POC. However, some chips lack sample preparation or require additional instrumentation, which is not suitable in resource-limited settings for POC. Moreover, due to the high contagious rate and characteristics of the multiple EBOV subtypes, low-cost multiplex detection chips should be developed.

2.2. Human immunodeficiency virus (HIV)

HIV is a single-stranded RNA virus that results in acquired immunodeficiency syndrome (AIDS) (Watts et al., 2009). HIV attacks T lymphocytes and integrates into the chromosomes of its host, which in turn leads to defects in the human immune system causing irreparable damage to the body (Druce et al., 2016; Kuznetsov et al., 2003; Shourian

and Qureshi, 2019). More than 37 million people live with HIV and infect about 2 million more every year (Anampa et al., 2020). This has been occurring since the first case of HIV infection in the early 1980s (Bao and Shao, 2018). Early HIV diagnosis can reduce transmission through behavioral preventive measures and aid in the treatment of infected individuals through treatment strategies such as anti-retroviral therapies (ART) (Choi et al., 2014). However, only 10%–51% of infected individuals are aware they are infected, most of who live in resource-limited areas where they are not able to readily be tested (WHO, 2010). Therefore, POC for early diagnosis of HIV is particularly important.

Investigators have applied microfluidics to POC for HIV and achieved encouraging results (Mauk et al., 2017). Glynn et al. (Glynn et al., 2014) reported a microfluidic chip based on the number of $CD4^+$ cells and magnetophoresis to detect AIDS (Fig. 4 A). This chip uses $CD4^+$ cell numbers to judge HIV infection in the blood and contains a capture efficiency of 93.0%. It does not need an additional pump and can be operated manually. Liu et al. also proposed microfluidic chips based on the number of CD4 + cells as well as immunomagnetic separation to detect HIV infection. However, DNA content was used to quantify $CD4^+$ cells. This chip can obtain accurate results from 10μL of whole blood, which is consist with flow cytometry analysis. Based on the principle of CD4 + cell detection, Alere Pima ™ CD4 was launched in 2010 and provides results within 20 min.

RT-LAMP is widely used for the detection of HIV RNA in a microfluidic system (Jangam et al., 2013; Sun et al., 2013; Zanoli and Spoto, 2013). Damhorst et al., (2015) developed a microfluidic platform that integrated RT-LAMP and the smartphone to detect HIV load (Fig. 4 B). Cell lysis buffer combined with a microfluidic chip was used to treat whole blood and complete RT-LAMP On-chip. As long as a concentration of 670 viral particles are contained in each microliter of whole blood, the virus can be detected. In more recent studies, Phillips et al. (Phillips et al., 2019) engineered an autonomous analysis device (microRAAD) instrument that detects HIV in whole blood (Fig. 4 C). A lateral flow immunoassay (LFIA) was used to visualize the product of RT-LAMP. This instrument achieves a limit of detection (LOD) of 100 HIV-1 RNA copies within 90 min. Chen et al. (Chen et al., 2016) developed a chip that can detect anti-HIV antibodies and HIV RNA, simultaneously. This chip meets serological requirements and detects HIV RNA as low as 10^3 viral particles/ml from saliva or blood.

Paper-based microfluidics is also an effective tool for HIV detection. Zhao and Liu, (2016) proposed a paper electrochemical microfluidic system for the diagnosis of an HIV/HCV co-infection. This paper system contains multi-channels and uses ELISA to detect antibodies in serum samples. This system can detect 300 pg/ml HIV and 750 pg/ml Hepatitis C virus (HCV) within 20 min. Kurdekar et al. (Kurdekar et al., 2016) use carbon dots, Whatman filter paper and nitrocellulose paper to detect the HIV antigen. Results suggest that assays using nitrocellulose paper have higher detection ranges (10 μg/mL to 250 pg/mL) and sensitivities (fourfold) compared to assays using Whatman filter paper. Li et al. (Li and Liu, 2016) (Fig. 4 D) developed an origami nanobiosensor based on paper and zinc oxide nanowires (ZnO NWs) to detect HIV. ZnO NWs was used to increase the surface area of electrodes as well as binding capacity. This biosensor utilizes an electrochemical impedance spectroscopy (EIS) method to achieve a LOD of 60 fg mL^{-1}. In addition, OraQuick®, developed by OraSure Technologies™, can detect the HIV antibodies in saliva and the specificity can reach 99.98%.

With the goal of detecting HIV, these studies were mainly performed analyzing CD4 + cells, nucleic acids and antigen-antibody reactions in microfluidic chips. Other methods such as RPA (Crannell et al., 2014; Lillis et al., 2016) and helicase dependent amplification (HDA) (Jordan et al., 2012) are also available in microfluidic chips. These chips demonstrate quicker detection speeds, lower detection limits and more optimal portability when compared to traditional laboratory methods. However, some chips do not integrate sample preparation and are not suitable for POC. Moreover, based on the presence of a maternal

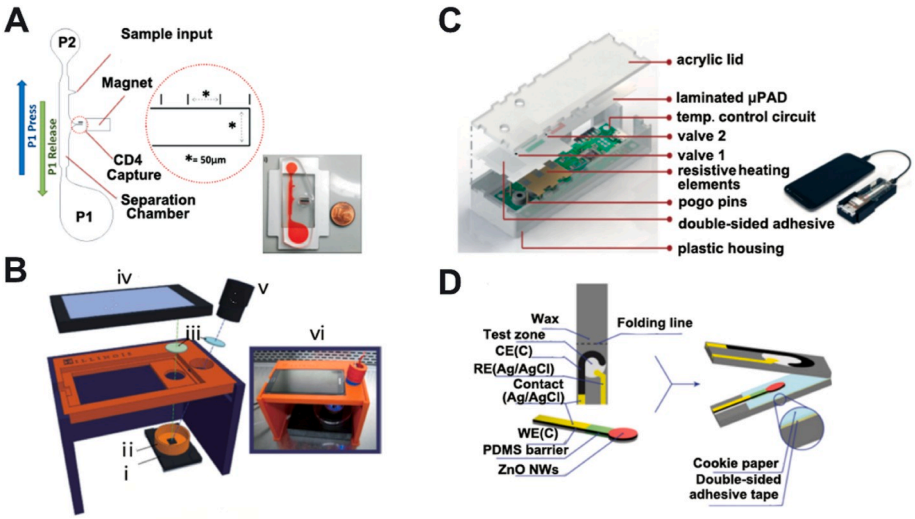

Fig. 4. Microfluidic systems for the detection of HIV. A: Schematic and photograph of the manual magnetophoretic $CD4^+$ isolation chip proposed by Glynn et al. Prior to the test, the chip was perfused through a degassing process. Direction of flow when P1 is depressed or released is indicated with blue and green arrows, respectively. Adapted from ref. 75 with permission from the Royal Society of Chemistry. B: Schematic and photograph of the RT-LAMP substrate and smartphone apparatus for HIV testing (Damhorst et al., 2015). (i) heating stage. The microfluidic chip was put on the stage (ii) copper base containing mineral oil, (iii) wavelength filters placed in front of the LED and smartphone camera, (iv) smartphone,(v) blue LED light source, and (vi) apparatus. Adapted from ref. 79 with permission from the Elsevier. C: Schematic and photograph of microRAAD for HIV testing (Phillips et al., 2019). When using this system, 1) the paper-based chip should be assembled into plastic housing with a temperature control circuit, 2) buffer should be added into inlets and sealed with adhesive tape to minimize evaporation, 3) the chip should be connected with a phone to heat, 4) one should wait 90 min for automated fluid delivery and sample incubation in μPAD, and 5) results should be analyzed. Adapted from ref. 80 with permission from the Royal Society of Chemistry. D: Schematic of a paper-based chip for the detection of HIV developed by Li et al. Image shows the components (left) and the assembly (right) of origami chip.Adapted from ref. 84 with permission from the WILEY-VCH. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

antibody or absence of a host antibody, methods to detect antibodies cannot be used to accurately diagnose HIV early (Rosenberg et al., 2015; Shafiee et al., 2015; Yan et al., 2019). Therefore, more innovative microfluidic technologies need to be developed, specifically ones that are user-friendly and affordable.

2.3. Influenza virus

The influenza virus results in significant morbidity and mortality causing a major public health concern worldwide (Bedford et al., 2015). The virulence of the influenza virus is reflected in the immunogen of its enveloped protein (Kaiser, 2006). Infected individuals suffer from severe viral pneumonia and acute lung injury (Guo and Thomas, 2017). The WHO estimates that influenza viruses infect approximately 5–15% of the world population and cause 250,000–500,000 deaths each year (Vemula et al., 2016). There are four types of influenza viruses including influenzas A, B, C and D. Among these, influenza virus A infects humans and other animals such as pigs and birds. Influenza viruses B and C only infects humans. Influenza virus A can be presented in 144 various subtypes based on combinations of 18 hemagglutinin (HA,H1–H18) and neuraminidase (NA,N1–N11) (Petrova and Russell, 2018; Tewawong et al., 2017). To prevent the spread of influenza and reduce economic and health burdens, accurate and rapid detection methods for the virus are necessary.

Currently, the influenza virus is a health concern for "lab on a chip" (Anderson et al., 2019; Singh et al., 2017; Vemula et al., 2016; Xu et al., 2010; Zhu et al., 2020). In 2016, Lee's group developed an integrated microfluidic method based on the sandwich-based aptamer that could detect H1N1 at a LOD of 0.032 hemagglutination units (HAU) within 30 min (Tseng et al., 2016). In 2020, their group (Lu et al., 2020) also proposed a more automated digital microfluidic platform to detect H1N1 (Fig. 5 A). This method utilizes electromagnetically-driven magnetic beads and enzyme-linked immunosorbent (ELISA)-like assays on the platform to detect H1N1 viruses. This system can also reach a LOD of 0.032 HAU within 40 min. Ma et al., (2019) proposed a simple self-driven microfluidic chip to detect H1N1 (Fig. 5 B). This system integrated nucleic acid extraction and RT-LAMP and was able to detect 3 $\times$ 10^{-4} HAU units/reaction in 40 min through colorimetric detection. Xia et al., (2019) developed a smartphone-based microfluidic system for the detection of avian influenza virus. This system uses gold nanoparticles to detect virus at aLOD of 2.7 $\times$ 10^{4} EID_{50}/mL.

The various characteristics of the multiple influenza virus strains make development of microfluidic systems more complicated (Zhang and Miller, 2019). More recently, Han et al., (2016) reported a microfluidic electrochemical system to multiplex detect the influenza A virus. This group established the electrochemical immunosensor through three electrodes arrangements and ZnO nanorods (NRs) on the inner surface of PDMS. This system can simultaneously detect the H1N1, H5N1 and H7N9 viruses in the 1 pg/ml - 10 ng/ml range. Wang et al., (2020) developed a microfluidic system based on magnetism mediated separation and size mediated signal detection to multiplex detect influenza A (Fig. 5 C). The LOD of this system reaches 3.4 ng/mL for H7N9 HA and 4.5 ng/mL for H9N2 HA. The disc chip proposed by Liu et al., (2018) can detect three avian influenza viruses and two influenza viruses on a single chip within 70 min. Shen et al., (2019) also proposed an integrated microfluidic system that contains sample preparation and a RT-PCR module (Fig. 5 D). This system uses glycan-coated magnetic beads to capture all influenza viruses in samples and can simultaneously detect twelve influenza subtypes with LODs ranging from 40 to 3000 copies within 100 min. Wu et al., (2019) developed a digital microarray system to multiplex detect H9N2, H1N1 and H7N9 avian influenza viruses. This system uses antibodies to modify the microarray fluorescent magnetic nanospheres to achieve multiplex detection with a LOD of 0.02 pg/mL. The commercial product Cobas® has been used for the detection of

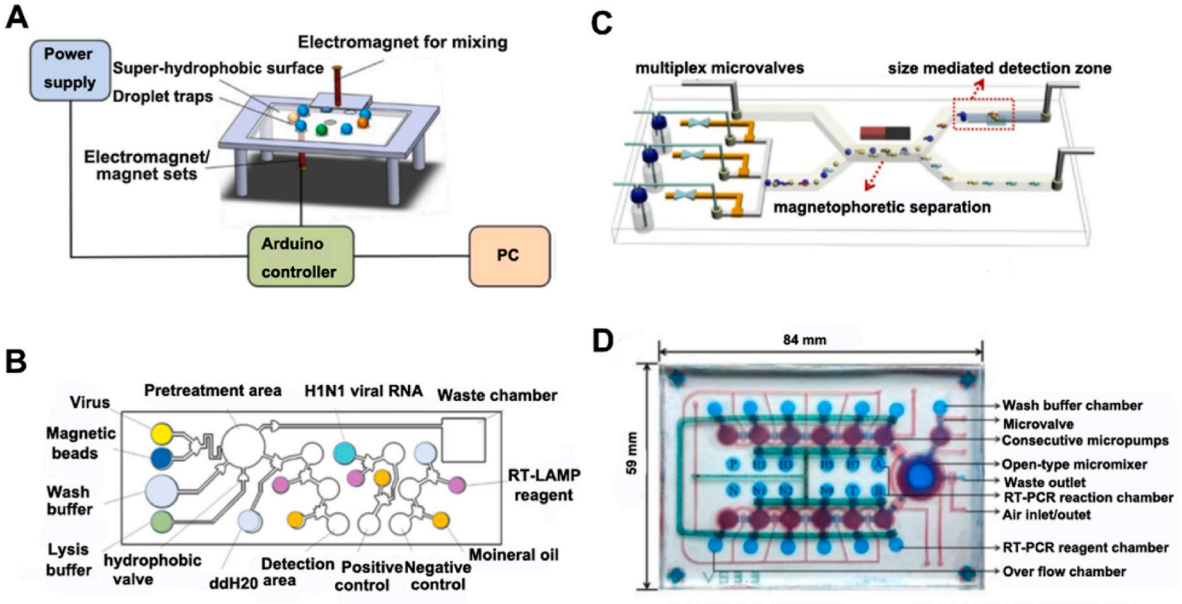

Fig. 5. Microfluidic systems for the detection of influenza virus. A: Schematic diagram of the integrated digital microfluidic platform for H1N1 detection (Lu et al., 2020). This platform is composed of a structure-free chip with a super-hydrophobic surface and relatively hydrophilic sets, an electromagnet driving system for the operation of droplets and beads, an electromagnetic mixer for liquid mixing and a control system including a power supply, a laptop and a microcontroller. Adapted from ref. 101 with permission from the Royal Society of Chemistry. B: Microfluidic chip developed for the detection of H1N1 (Ma et al., 2019). This is a self-driven, passive microfluidic chip that can perform sample pretreatment, RT-LAMP and H1N1 viral detection on a single chip. Adapted from ref. 102with permission from the Elsevier. C: Schematic illustration of the microfluidics platform for the detection of H7N9 and H9N2 (Wang et al., 2020). This is a magnetism and size mediated platform. Different influenza subtypes could be simultaneously separated and detected depending on the different-sizes magnetic beads. Adapted from ref. 106 with permission from the Elsevier. D: Photograph microfluidic chip for the detection of 12 influenza subtypes (Shen et al., 2019). Arrayed reaction chambers contain primer sets for amplifying specific regions of the HA and NA genes such that the RT-PCR-derived signal output could be used for viral subtyping. P: positive control chamber; N: negative control chamber; T: temperature measurement chamber. H and N represents different subtypes. Adapted from ref. 108 with permission from the Royal Society of Chemistry.

influenza. This instrument uses qRT-PCR detection, which can detect and distinguish between influenza A and influenza B viruses within 20 min using RNA detection of nasopharyngeal swab specimens.

Microfluidic chips have widely focused on the detection of influenza viruses. Both detection time and LOD have significantly improved through this advanced technology. Since there are various subtypes of the influenza viruses, multiplex detection ability of these chips still need improvement. Moreover, rapid and ongoing evolution of influenza viruses will make this even more challenging. Furthermore, portability and cost should be further improved since influenza viruses are common and universal.

2.4. Zika virus (ZIKV)

ZIKV is a single-stranded, RNA virus that belongs to flaviviridae and is a causative agent of Zika fever (Metz et al., 2019; Qadir et al., 2018). This mosquito-borne virus was identified in 1947 (Nicolini et al., 2017) and 84 countries so far have been affected (Nelson et al., 2019). The WHO has announced that ZIKV is a PHEIC (Xu et al., 2016). ZIKV can be transmitted through human contact and has been detected in urine, blood, semen, amniotic fluid, cerebrospinal fluid, saliva and even tears (Paixao et al., 2016; Wu et al., 2018). ZIKV infection is generally asymptomatic. A small number of people will have mild clinical symptoms such as mild fever, fatigue, headache, joint pain and a rash, which will rarely lead to serious illness or complications. In recent years, it has been found that the virus can cause teratogenicity and Guillain-Barre syndrome (Cugola et al., 2016; van den Berg et al., 2014). The high contagious rate of the virus led to over 2 million humans being infected globally (Santiago et al., 2018). The most recent outbreak (Petersen et al., 2016) highlights that early diagnosis of ZIKV is extremely important to control epidemic situations, which is extremely challenging (Janahi et al., 2017; Ricotta et al., 2019).

In recent years, microfluidics has also shown to be an effective tool for the early diagnosis of ZIKV. Microfluidic chips based on nucleic acid detection have important applications in ZIKV detection (Pardee et al., 2016). For example, Song et al., (2016) reported a cassette microfluidic system based on RT-LAMP (Fig. 6 A). This chip is chemically heated to eliminate the need for electricity. Moreover, it uses a visualization method to observe the virus. These characteristics make this system extremely suitable for POC. This system also achieved detection of 5 plaque-forming units (PFU) in 40 min. Ganguli et al., (2017) generated a microfluidic chip based on a RT-LAMP and smartphone combination. This chip has the ability to multiplex detect ZIKV and other viruses for precise results. The LOD of this system is $1.56e^5$ PFU/mL in blood under 35 min. Kaarj et al., (2018) developed a paper microfluidic chip combined with RT-LAMP and a smartphone to detect ZIKV RNA. This system is sensitive and can detect 1 copy/μL in 15 min with high specificity. However, this system requires additional purification steps. Yang et al., (2019) proposed a wearable microfluidic system to detect the Zika virus (Fig. 6 B). This system integrates RPA on a bandage-like sensor. Body heat can activate the sensor since the RPA can react at room temperature. It has also been demonstrated that the wearable biosensor reaches a detection limit of 10 copies/μL within 10 min. This method has proven to be very convenient, low-cost and easy-to-receive. If equipped with a sample preparation function in the future, it will have very broad application value. More recently, Batule et al. (Batule et al., 2020) reported a two-step paper chip strategy used for RNA extraction and RT-LAMP. This method can detect 10 copies in the serum within 1 h.

On-chip immunological testing remains an important diagnostic measure for Zika virus infection. Draz et al., (2018) reported a paper chip that used platinum nanoparticles. The platinum nanoparticles used antibodies on paper that improved sensitivity and specificity. This chip

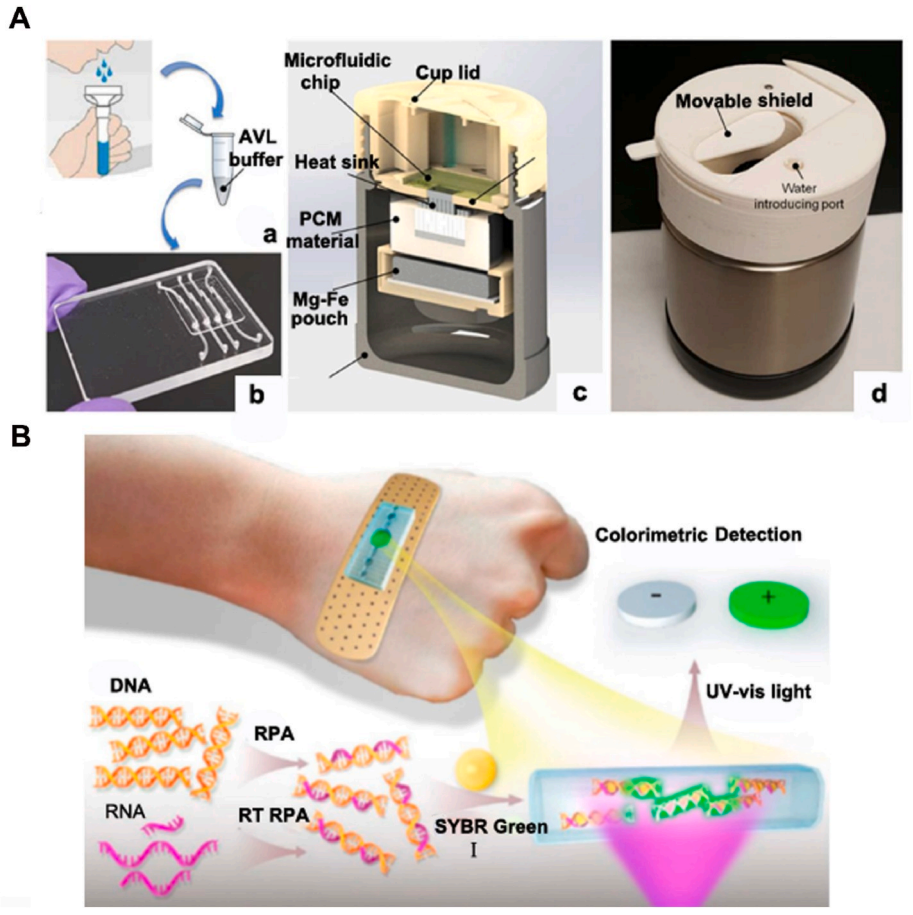

Fig. 6. Microfluidic systems for the detection of ZIKV. A: Workflow of the portable cup device based on the microfluidic system developed by Song et al. (a) Schematic of saliva sample preparation. Saliva samples are collected in a saliva collection tube and then lysed in Qiagen binding/lysis (AVL) buffer. (b) The lysed sample is filtered through the isolation membrane of a microfluidic cassette for nucleic acid extraction. (c) Enlarged view of the chemically-heated cup. The cup consists of a thermos cup body, a 3Dprinted cup lid, a chip holder, PCM material, heat sink and single-use Mg–Fe alloy pack heat source. (d) A photograph of the chemically-heated cup for point of care molecular diagnostics of ZIKV. Adapted from ref. 120 with permission from the ACS publications. B: Schematic of the wearable microfluidic sensor for detection of ZIKV nucleic acids (Yang et al., 2019). The detection method was based on the RPA. The reaction can start on this wearable microfluidic system effectively by human epidermal heat that was close to the optimal temperature of RPA. Adapted from ref. 123 with permission from the Elsevier.

was able to detect ZIKV with a LOD of 10^1 copies/μl. Rong et al., (2019) developed a paper microfluidic system based on quantum dot probes and smartphones. This chip shows limited cross-reactivity with other viruses and can reach a LOD of 0.15 ng/mL in serum within 20 min. Meena et al., (2018) developed an optofluidic chip based on magnetic beads and optical detection to simultaneously detect ZIKV nucleic acids and proteins. This method contained a LOD of 8 fm and ruled out potential interference from other viruses.

Microfluidic technology has provided a new route for the detection of ZIKV. Although qRT-PCR is still the gold standard for ZIKV detection, microfluidics has shown fast and accurate advantages and continued development will demonstrate their practical utility in response to ZIVK outbreaks. In addition, compared to other viruses such as EBOV and the influenza virus, ZIKV does not have multiple subtypes. However, to date, ZIKV infection is still difficult to diagnose because of its cross-reactivity with other flaviviruses, such as dengue virus (Wu et al., 2018). Therefore, in the continued development of improved microfluidic methods, the detection of other flaviviruses or arboviruses need to be ruled out for cross-reactivity (Chang et al., 2017).

2.5. Dengue virus (DENV)

DENV is a mosquito-borne virus that causes dengue fever (DF), dengue hemorrhagic fever and dengue shock syndrome (DSS) (Lang et al., 2016; Nakhapakorn and Tripathi, 2005). DENV belongs to the flaviviridae group and has four serotypes (DENV1-4) (Zonetti et al., 2018). Dengue fever usually has a 10-day incubation period. Patients usually have typical symptoms such as fever, severe headache, post-ophthalmic pain, muscle and joint pain, a rash, nausea, abdominal pain and swollen glands (Adimy et al., 2020; Chan and Johansson, 2012; Halstead, 2008). Currently, the main detection methods used in laboratories for dengue virus rely on cell culture, PCR and ELISA assays. These time time-consuming, low sensitivity methods cannot quickly respond to DENV outbreaks (Suthanthiraraj et al., 2019).

Microfluidic based methods can give more precise and efficient results compared to electrochemical methods for the early detection of DENV (Eivazzadeh-Keihan et al., 2019). Recently, Yoo et al., (2020) proposed a microfluidic system that integrated direct sample preparation and LAMP to detect dengue virus (Fig. 7 A). This strategy used bead beating and heating procedures to obtain stable RNA directly from whole blood, which could be used to detect viruses. In this system, direct buffer was used to extract RNA from whole blood and obtain a LOD of 10^2 PFU/200 μL in less than 1 h. Yin et al., (2020) reported a microfluidic system that integrated RNA extraction and multiplex PCR to detect four DENV serotypes (Fig. 7 B). In this system, chitosan-modified paper chip to extra RNA and on-chip PCR product was detected using a membrane sensor. This system detected 100 RNA copies per mL of plasma within 90 min. Choi et al., (2017) developed a paper chip that applied agarose into paper to achieve flow control and improve detection sensitivity (Fig. 7 C). Moreover, this chip integrated RNA extraction and RT-LAMP to detect DENV RNA in blood samples. Using this chip, DENV RNA was detected at 50 RNA copies.

Non-structural protein 1 (NS1) antigen detection was universally used in serological tests for DENV. NS1 is a highly conserved glycoprotein with a molecular weight of 45–55 kDa (Lai et al., 2019). For immunological tests on chip, Hosseini et al., (2015) fabricated a disk chip equipped with polymethacrylate microspheres and microballoon mixing systems. This chip can manipulate 54 samples in parallel and can detect 1.9 pfu/mL in serum. A dielectrophoresis chip was also proposed by Iswardy et al., (2017) (Fig. 7 D). A dielectrophoresis force was used in this chip to capture beads and an immunoreaction was used to capture the virus. This chip only requires 5 min to detect the virus with a LOD of 10^4 PFU/mL from 15 μL samples. Yu-zoon et al. (Yuzon et al., 2019) generated a paper chip using cellulose acetate film and a nitrocellulose membrane to detect the NS1 antigen. This chip reached a LOD 84.66 ng/mL in 2 min.

Microfluidics can be regarded as a capable candidate of POC for DENV. Since DENV easily cross-reacts with ZIKV, multiplex and precise

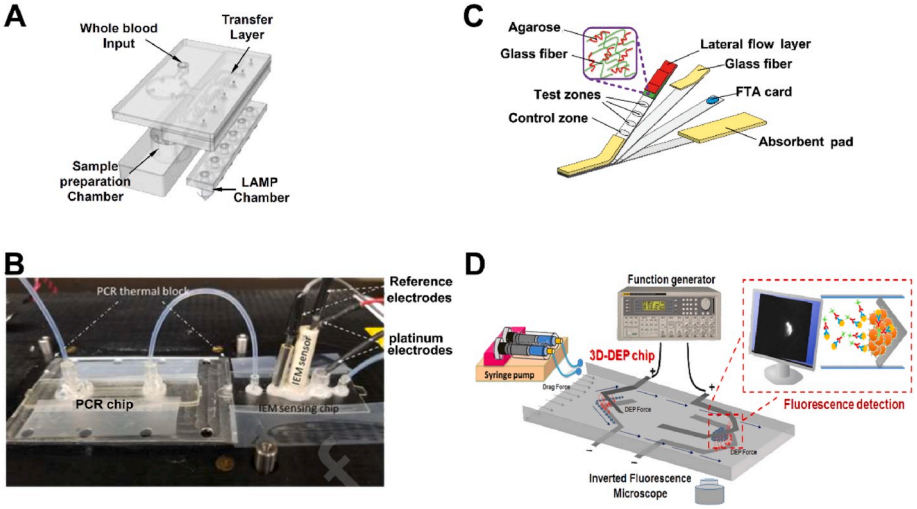

Fig. 7. Microfluidic systems for the detection DENV. A: Schematic and function of microfluidic chip for DENV detection in whole blood (Yoo et al., 2020). This chip integrated RNA extraction and LAMP for the detection of DENV. The authors use direct buffer, bead beating and mild heating for the amplification of RNA from virus in whole blood. Adapted from ref. 133 with permission from the Royal Society of Chemistry. B: Photograph of the polycarbonate based microfluidic sensing chip for detection of 4 DENV serotypes (Yin et al., 2020). The platform consists of a filter paper-based sample pretreatment unit capable of capturing nucleic acid molecules for downstream PCR amplification, an on-chip PCR unit to amplify the target DENV RNA serotypes and an IEM based sensor to detect amplified products. Adapted from ref. 134 with permission from the Elsevier. C: Schematic of the paper chip for detection of DENV developed by Choi et al. This is a sensitive and semi-quantitative sample-chip with multiple test zones. The lateral flow layer is for target detection. The glass fiber is designed for amplification. The FTA card is used for RNA extraction. Adapted from ref. 135 with permission from the WILEY-VCH. D: Schematic of the microfluidics dielectrophoresis chip (Iswardy et al., 2017). The dielectrophoresis force was used to capture beads (mouse anti-flavivirus monoclonal antibody-coated beads) in microfluidic chips and the DENV modified with fluorescence labels and then were captured on modified beads by immunoreactions. Fluorescence microscopy was used to capture signals. Adapted from ref. 138 with permission from the Elsevier.

detection in microfluidics should be improved. Moreover, the four serotypes of DENV should be considered when novel chips are developed in the future.

2.6. COVID-19 and commercialized products

In the 21st century, two highly pathogenic human coronaviruses including Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) have emerged and triggered global pandemics that resulted in high morbidity and mortality. COVID-19 is also a type of coronavirus that belongs to the β-Coronavirus (Kim et al., 2020). Currently, COVID-19, which is caused by the severe acute SARS-CoV-2, poses a major threat to human health as well as economies world-wide. SARS-CoV-2 is believed to infect host cells through the angiotensin-converting enzyme 2 (ACE2), resulting in COVID-19. SARS-CoV-2 has a stronger transmission capacity compared to SARS and has a similar pathogenicity compared to MERS-COV(Zheng et al., 2020). COVID-19 symptoms include a dry cough, fatigue and fever that is followed by anorexia, myalgia and dyspnea. In addition, COVID-19 can also cause damage to the myocardium, resulting in chronic cardiovascular issues (Li et al., 2020; Zheng et al., 2020). The WHO has declared the COVID-19 epidemic as a PHEIC on January 31, 2020. This virus has infected millions of people worldwide in just a few months. Nucleic acid detection has been used to detect the virus during this outbreak. The National Medical Products Administration (NMPA) announced nucleic acid testing as the gold standard for virus detection. Antibody testing is used as a supplementary test for suspected cases where nucleic acid detection was negative and is not used as a basis for initial diagnosis or exclusion of new coronavirus infection.

To detect the virus, qRT-PCR is still used as the mainstream detection method. However, due to the rapid development of the epidemic, qRT-PCR can no longer meet the demands associated with needed testing. POC instruments that based on the microfluidic technology play important roles in diagnosing the virus during this epidemic. For example, The ID NOW® instrument proposed by Abbott™ in USA can detect positive samples in 5 min and negative results in 13 min. This product has received emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA). The detection principle is based on the RPA technology and the instrument only weighs 3 kg, which is very suitable for POC. Filmarray®, a product of BioFire™, uses microfluidic technology that integrates nucleic acid extraction, purification and PCR amplification into a single chip and results in sequential and accurate detection. This instrument has been previously used for the detection of EBOV. Currently, the COVID-19 test kit has been approved by the FDA for EUA based on this system and can be used for rapid detection. The test is specifically designed and ran on existing Filmarray® 2.0 and Filmarray® Torch platforms. GeneXpert® developed by Cepheid™ can integrate sample preparation, nucleic acid amplification and detection into a small detection kit, where even those without professional skills can perform complex molecular detection analyses. This system has been used for the detection of HIV. In response to COVID-19, Xpert SARS-CoV-2 nucleic acid detection reagent has obtained EVA from FDA for the qualitative detection of SARS-CoV-2 nucleic acid. RTisochip® proposed by CapitalBio™ in China can detect 6 common respiratory viruses including COVID-19 in a single chip within 1.5 h. This system not only detects SARS-CoV-2, but also effectively identifies patients with influenza and COVID-19. The POC instrument developed by Cannon™ in Japan can detect the SARS-CoV-2 in 35 min. The instrument only weighs 2.4 kg and DNA can be amplified in as little as 10 min using respiratory samples.

Microfluidic technology can both be automated and miniaturized to detect viruses. This advanced technology in POC will change current medical methods. Compared to the SARS-CoV and MERS-CoV outbreaks, lab on a chip has played a crucial role in the COVID-19 outbreak. Countries including the USA, China and Japan have approved the use of this technology, which fully demonstrates the application value of lab on a chip in POC.

2.7. Other representative viruses

HBV is highly contagious and spreads through bodily fluids such as blood, saliva and semen. HBV infection can cause cirrhosis, liver failure or hepatocellular carcinoma (Estevez et al., 2017; Lavanchy, 2004; Sarrazin, 2016).Investigators also use microfluidics to perform convenient and accurate diagnoses for these viruses (Chang et al., 2015; Vaghi et al., 2016). Li et al. (Li et al., 2019b) described a disc chip to detect HBV in whole blood. This disc chip integrated sample preparation and qRT-PCR. Detection reagents were prestored into the chip and the freeze-dried reagents were kept in 2–8 °C for 6 months in the disc chip. Moreover, the separation step of plasma or serum is avoided since it is directly detected from whole blood. This system can detect 10^2 copies/mL HBV DNA in ~48 min from 500 μL of whole blood. Our group also proposed a digital isothermal chip for the quantitative detection of HBV. This chip has 120576 reaction chambers and the dynamic range of the detection template is up to 6 orders of magnitude. The maximum detectable template amount is 1.13×10^6 copy numbers in 36 μL (Wu et al., 2017). Hepatitis C (HCV) is the major cause of chronic liver disease and is often associated with the development of liver cirrhosis, hepatocellular carcinoma, liver failure and death (Pawlotsky, 2016; Petruzziello et al.). Mu et al., (2014) developed a paper chip to detect HCV(Fig. 8 A). This method was based on the detection IgG antibodies against HCV and an 8-plex paper chip was designed to yield additional information about the HCV infection. On this chip, 267 amol was detected using chemiluminescence and 26.7 fmol was detected using colorimetry.

African swine fever virus (ASFV) is a large double stranded DNA virus that contains a high mortality rate in domestic pigs and wild boar (Hubner et al., 2018). Virulence can be divided into high, moderate, low and without clinical symptoms. High virulence ASFV can lead to the rapid death of infected animals, where moderate or low virulence may lead to a persistent infection and continuous detoxification (Nurmoja et al., 2017; Tulman et al., 2009). Recently, He et al., (2020) developed a cartridge system that uses CRISPR-Cas12a and CRISPR RNA to detect ASFV DNA. Using this method, the amplification of nucleic acid is not needed. The LOD of this system is 1pm in 2 h and 100 fM in 24 h. Ye et al., (2019) proposed a portable disc system (Fig. 8 B)to detect the ASFV using a circular fluorescent probe-mediated isothermal nucleic acid amplification (CFPA) method. This system has a LOD of 10 copies/μL and 100% specificity for pig samples in 10.8 min.

3. Challenges in using microfluidics for viral detection

3.1. Integrated sample preparation

Sample preparation is crucial for precise virus detection. Microfluidic systems even have quicker and more accurate advantages compared to traditional methods when it comes to virus outbreaks, where many of these methods ignore sample preparation, which is not suitable for POC. In addition, compared to other detection objects, nano-level and RNA-coded viruses pose greater challenges for sample preparation. In recent years, virus sample preparation has also attracted more attention and there have been different proposals for viral sample preparation strategies. For different detection methods, sample preparation have different meanings such as sample enrichment (Surawathanawises et al., 2016) or nucleic acid extraction (Chen et al., 2019; Zhang et al., 2019). Recently, Du et al. (Du et al., 2017a) proposed an automated sample preparation microfluidic system that utilized air bubbles and magnetic beads to achieve efficient capture of the Ebola virus. Vaghi et al., (2016) reported a PDMS chip for HCV RNA purification and detection from plasma. Capture efficiency was improved with two orders of magnitude and LOD was improved 10-fold using this system. Kim et al., (2019) proposed a microfluidic system to concentrate

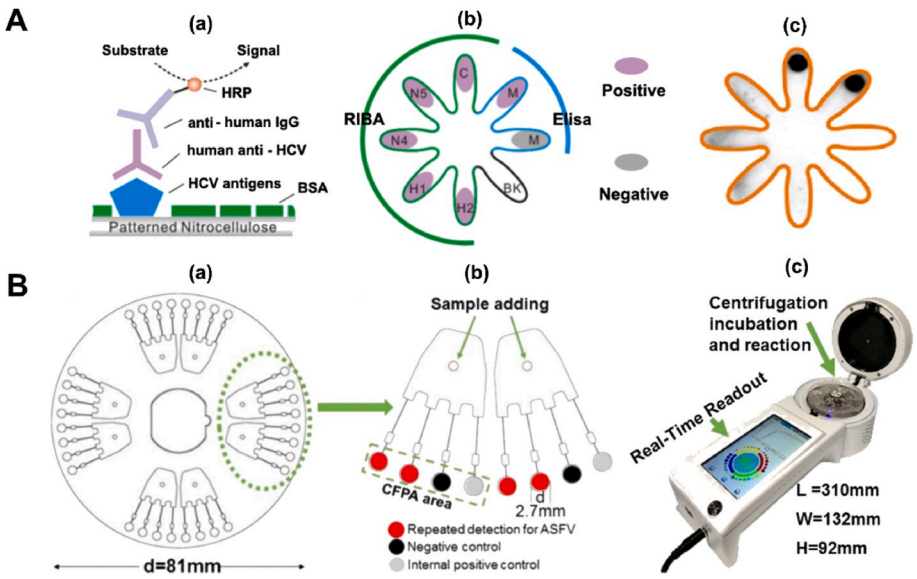

Fig. 8. Microfluidic chip for the detection of HCV and ASFV. A: The multiplex chip for the detection of HCV developed by Mu et al. a: Schematics of indirect ELISA procedures. The labeled horseradish peroxidase (HRP) could catalyze the substrate and generate signals. The individual recombinant HCV antigens or the equal mixtures are immobilized on specific detection zones. b: Schematic illustration of the combination of segmented ELISA and recombinant immunoblot assays (RIBA). The immobilized antigens were labeled (M: mixture of antigens; C: Core; N5 and N4 for NS5 and NS4, respectively; H1 and H2: human IgG antibody at different concentrations; BK: Blank). The human IgG antibody could capture human IgG in serums for positive control. c: chemiluminescence image of different concentrations. Adapted from ref. 145 with permission from the ACS publications. B: The disc chip for the detection of ASFV (Ye et al., 2019). A: schematic of the disc chip; (B) Detailed view of the chip with its sample adding area, channels, and reaction area; The four reaction holes include one negative control, one internal positive control (a house-keeping gene from the pig genome) and two repeated experiments for the detection of the ASFV (C) Photograph of the portable hand-held device (310 × 132 × 92 mm). Adapted from ref. 149 with permission from the ACS publications.

viral particles. In this system, the poly (ethylene glycol) methacrylate (PEGMA) membrane was integrated into the chip and the virus was concentrated through autonomous and continuous perfusion. Yeh et al. (Yeh et al., 2020)developed a microfluidic chip for rapid virus capture and *in situ* detection. This chip uses carbon nanotube arrays with differential filtration porosity to concentrate the virus and uses surface-enhanced Raman spectroscopy (SERS) to detect the virus. This research demonstrates that an effective virus sample preparation method in chip will give more precise results.

In addition, the integration of sample preparation with detection is important especially for nucleic acid-based detection methods (Yin et al., 2019). However, very few studies have been able to integrate virus sample preparation into chips. Integrated sample preparation will reduce testing time, improve accuracy and minimize labor. Moreover, sample-in-answer-out is the ideal detection process. Therefore, sample preparation should be considered in a single chip. Whether Lab-on-a-chip is used in the clinic or the home, sample preparation integration is necessary. In addition, affordable and user-friendly qualities should be considered especially for POC in resource-limited settings. Automated and high-throughput microfluidics should also be considered. Therefore, additional sample preparation methods should be tested and integrated into chips that will be used for virus outbreaks.

3.2. High throughput and multiplex detection

Virus outbreaks are characterized by a rapid spread and large scale infection. For example, DENV causes 50–100 million infections, with ~2.5% of individuals passing away (Yu et al., 2015). SARS-CoV-2 has spread to 25 countries across 4 continents and over 40,000 cases have been confirmed in only 3 months (Li and De Clercq, 2020). These characteristics pose a huge challenge for detection methods. The gold standard detection method qRT-PCR can achieve a throughput of 96 or 384 samples (Bustin and Mueller, 2005), which is higher than current microfluidic-based methods. Moreover, studies have shown that when there is a viral outbreak, increased deaths are due to a large number of infections, not increased toxicity (Harris et al., 2008). Therefore, microfluidic chips used for clinically-oriented virus detection face a throughput challenge.

Multiplex detection can improve the accuracy of early detection (Seok et al., 2017) and give additional details for infected patients (Goktas and Sirin, 2016) since most viruses have various subtypes and pathogenicity. However, many studies have ignored the fact that there are virus subtypes and only target one or more subtypes, which affects accuracy in practical applications. For example, some viruses such as influenza virus have nearly 200 subtypes, which poses a great challenge for microfluidic chip. To achieve multiple detection in chips, multiple colors or different division areas are used (Gu et al., 2018; Pang et al., 2018; Yan et al., 2017; Zhang et al., 2016). However, these methods generally need expensive instrument and reagents, which limit the application of the chip. Therefore, multiple detection capabilities are challenges in the clinical application of microfluidic chip.

3.3. Quantitative methods

The development of microfluidic technology makes "sample-in-answer-out" possible for virus detection. Most research and commercial products obtain results according to the standard curve, which is a relative quantitative method. This type of quantitative method is often limited by several factors including inhibitors and amplification efficiency (Bian et al., 2015). Digital quantitative methods such as digital PCR and digital LAMP can achieve absolute quantification and do not depend on the standard curve to obtain high sensitivity (Sreejith et al., 2018). Recently, studies have shown the accuracy of digital quantitative methods and this emerged technology has been widely used in clinical diagnoses (Salipante and Jerome, 2019; Tian et al., 2015; Yin et al., 2019). However, due to limitations related to instruments, costs and sample preparation, it is difficult to apply this quantitative method in POCT. Therefore, the use of digital quantitative methods such as digital RPA and digital Elisa to achieve "sample-in-digital-answer-out" results pose great challenges in virus detection.

4. Summary

In this review, viral outbreaks were introduced as well as a discussion of the advantages and disadvantages of various microfluidic systems in response to these viruses. These life-threatening viruses have different characteristics that influence different microfluidic chips in early virus detection. In summary, after decades of work, microfluidic technology has made its breakthrough in LOD, time and speed for virus detection. This technology will significantly transform virus testing for POC in the

home or clinical settings. In addition, this article highlights the urgent challenges that microfluidic chips currently face when it comes to virus detection such as sample preparation integration, quantitative methods, the ability to perform throughput and multiplex during a virus outbreak.

5. Future perspectives

Despite many challenges, these technologies are gradually changing the POC of viruses. There has been some progress in the detection of viruses such as wearable chips, paper chips, disc chips and the emergence of commercial products such as the Filmarray®. To overcome these challenges, the material and design of microfluidic chips, the innovation of detection methods and the miniaturization of instruments need to all be improved, which requires collaboration between scientists with different expertise. In addition, research should not be limited to microfluidic technology. If the microfluidic chip is further combined with the "Biological mobile phone", "Mobile detection station", or "Artificial Intelligence", its potential for virus detection will be extended even further.

In the future, microfluidic products that meet the criteria for POC proposed by WHO including (1) being affordable to those at risk of infection, containing (2) high sensitivity, (3) high specificity, (4) user-friendly capabilities, being (5) rapid and robust, (6) equipment free, and (7) delivered to those who need it (Blacksell, 2012; Huppert et al., 2010; Tenforde et al., 2019) will be readily available. To apply microfluidic chips clinically, professional users can use microfluidic technology with simple operations and detect a large number of samples in a short time while obtaining accurate information. Early detection of viruses using microfluidic technology can help reduce the scale of viral outbreaks and improve response to infection.

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.

Acknowledgments

The authors are grateful for the financial support from the National Program on Key Research Project of China (SQ2019YFE010999) as well as European Union's Horizon 2020 Research and Innovation Program under Grant Agreement No 861917-SAFFI, the National Key R&D Program of China (2018YFF01012100), the Fundamental Research Funds for the Zhejiang Provincial Universities (2- 2050205-19-007) and the Open Research Project of the State Key Laboratory of Industrial Control Technology, Zhejiang University, China.

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