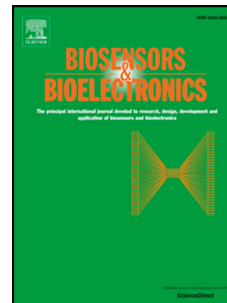# Journal Pre-proof

The potential of an integrated biosensor system with mobile health and wastewater-based epidemiology (iBMW) for the prevention, surveillance, monitoring and intervention of the COVID-19 pandemic

Kang Mao, Hua Zhang, Zhugen Yang

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1   **The potential of an integrated biosensor system with mobile health and**

2   **wastewater-based epidemiology (iBMW) for the prevention, surveillance, monitoring**

3   **and intervention of the COVID-19 pandemic**

4   Kang Mao[a], Hua Zhang[a*] and Zhugen Yang[b*]

5   *[a] State Key Laboratory of Environmental Geochemistry, Institute of Geochemistry, Chinese*

6   *Academy of Sciences, Guiyang, 550081, China*

7   *[b]Cranfield Water Science Institute, Cranfield University, Cranfield, MK43 0AL, United*

8   *Kingdom*

9

10   Corresponding Email: zhugen.yang@cranfield.ac.uk (ZY) zhanghua@mail.gyig.ac.cn (HZ)

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12   Contents

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23

24   **Abstract:** The outbreak of novel coronavirus pneumonia (COVID-19) has caused a significant public

25   health challenge worldwide. A lack of effective methods for screening potential patients, rapidly

26   diagnosing suspected cases, and accurately monitoring the epidemic in real time to prevent the rapid

27   spread of COVID-19 raises significant difficulties in mitigating the epidemic in many countries. As

28   effective point-of-care diagnosis tools, simple, low-cost and rapid sensors have the potential to greatly

29   accelerate the screening and diagnosis of suspected patients to improve their treatment and care. In

30   particular, there is evidence that multiple pathogens have been detected in sewage, including

31   SARS-CoV-2, providing significant opportunities for the development of advanced sensors for

32   wastewater-based epidemiology that provide an early warning of the pandemic within the population.

33   Sensors could be used to screen potential carriers, provide real-time monitoring and control of the

34   epidemic, and even support targeted drug screening and delivery within the integration of emerging

35   mobile health (mHealth) technology. In this communication, we discuss the feasibility of an

36   **i**ntegrated point-of-care **b**iosensor system with **m**obile health for **w**astewater-based epidemiology

37   (iBMW) for early warning of COVID-19, screening and diagnosis of potential infectors, and

38   improving health care and public health. The iBMW will provide an effective approach to prevent,

39   evaluate and intervene in a fast, affordable and reliable way, thus enabling real-time guidance for the

40   government in providing effective intervention and evaluating the effectiveness of intervention.

41   **Keywords**: point-of-use sensors, wastewater-based epidemiology, mobile health, pandemic, early

42   warning

1. Introduction

The COVID-19 pandemic caused by a novel coronavirus (SARS-CoV-2) has spread rapidly throughout more than 200 countries and has led to a worldwide disaster. Some dilemmas are associated with COVID-19 care and management from the initial outbreak to the present situation, some of which have been resolved and some of which have not (more detailed description is seen in Tab. S1). A good understanding of these dilemmas and putting forward solutions will help us face COVID-19 and novel infectious disease epidemics in the future. It is critical to adopt strict and accurate public health measures for COVID-19 care to address these difficulties and risks in the processes of prevention, diagnosis, intervention, and even therapy (Dowell et al. 2016).

Point-of-care (POC) biosensors may achieve the intended goal, enabling the convenient acquisition of both pathogen information and host-response information in almost any location in a short time, which has the potential to facilitate prevention and rapid diagnosis and intervention for COVID-19 when combined with other useful technologies. We discuss the feasibility of an **i**ntegrated POC **b**iosensor system with **m**obile health for **w**astewater-based epidemiology (iBMW) for early warning of COVID-19, screening and diagnosis of potential infectors, improving patient health care and monitoring public health.

2. iBMW for the prevention, surveillance, monitoring and intervention of the COVID-19 pandemic

2.1. Point-of-use biosensors for COVID-19 diagnosis

The first crucial step is the rapid and accurate diagnosis of COVID-19 to screen potential patients, confirm suspected cases, provide timely health care/treatment, monitor and manage the epidemic (Udugama et al. 2020). Biosensors offer great potential to meet diagnostic requirements (Part S1) and can be used to detect COVID-19-related indicators (Russell et al. 2020). Compared with traditional

66   detection methods, biosensors can provide a fast response time and ultra-low limit of detection,

67   enabling the potential for miniaturization and portable analysis but requiring minimal sample

68   processing (Veber and Weidermann 2018).

69   Biosensors are analytical devices with biological elements as receptors (e.g., antibodies, aptamer,

70   peptides, protein, etc.) that can generate physicochemical signals (optical, electrochemical, etc.) in the

71   presence of targets for biorecognition. Biosensors provide the possibility for rapid and real-time

72   diagnostic monitoring of COVID-19 to solve the current dilemma, as they have become a powerful

73   tool for detecting diseases (Mao et al. 2020a; Yang et al. 2017). In addition, this method can be used

74   to determine both pathogens and blood glucose, blood pressure, platelets and other indicators related

75   to the symptoms of COVID-19 (Yang et al. 2015b). Currently, there are many mature portable sensor

76   devices that perform real-time diagnosis and detection; these include thermometers to measure body

77   temperature and blood glucose meters to measure blood glucose and other conventional indexes.

78   There are significant opportunities for biosensors to contribute to the rapid diagnosis and screening of

79   infectious disease, in particular together with nanotechnology with an ultrasensitive detection of a

80   range of disease markers (Bhalla et al. 2020). However, the main difficulty is the need to quickly and

81   effectively detect specific indicators of infectious diseases, such as pathogens. The results of these

82   indicators will aid in the diagnosis of suspected and potential cases.

83   Biosensors have great potential for rapidly diagnosing infectious disease and for the determination

84   of infection transmission. For example, Trinh et al. constructed a foldable loop-mediated isothermal

85   amplification (LAMP)-based biosensor integrating nucleic acid purification, amplification, and a

86   detection method as a visual assay for multiple foodborne pathogens (Trinh and Lee 2019). Although

87   the genetic material of SARS-CoV-2 RNA is different from that of DNA-based pathogens, the sensor

88 also has the capability to rapidly diagnose COVID-19 through the detection of SARS-CoV-2 RNA

89 (Bhalla et al. 2020) (Pokhrel et al. 2020). For example, Lee et al designed an easy-to-operate and

90 highly sensitive analytical method for diagnosing the Zika virus through reverse transcription

91 (RT)-LAMP and a lateral flow test that can produce results within 35 min (Lee et al. 2016). For the

92 detection of another dangerous RNA-based virus pathogen, Ebola, Ahrberg et al designed a

93 palm-sized biosensor for rapid Ebola detection within 37 min (Ahrberg et al. 2016). These studies

94 demonstrated that the biosensor has a clear potential for the rapid detection of SARS-CoV-2 and

95 COVID-19 biomarkers.
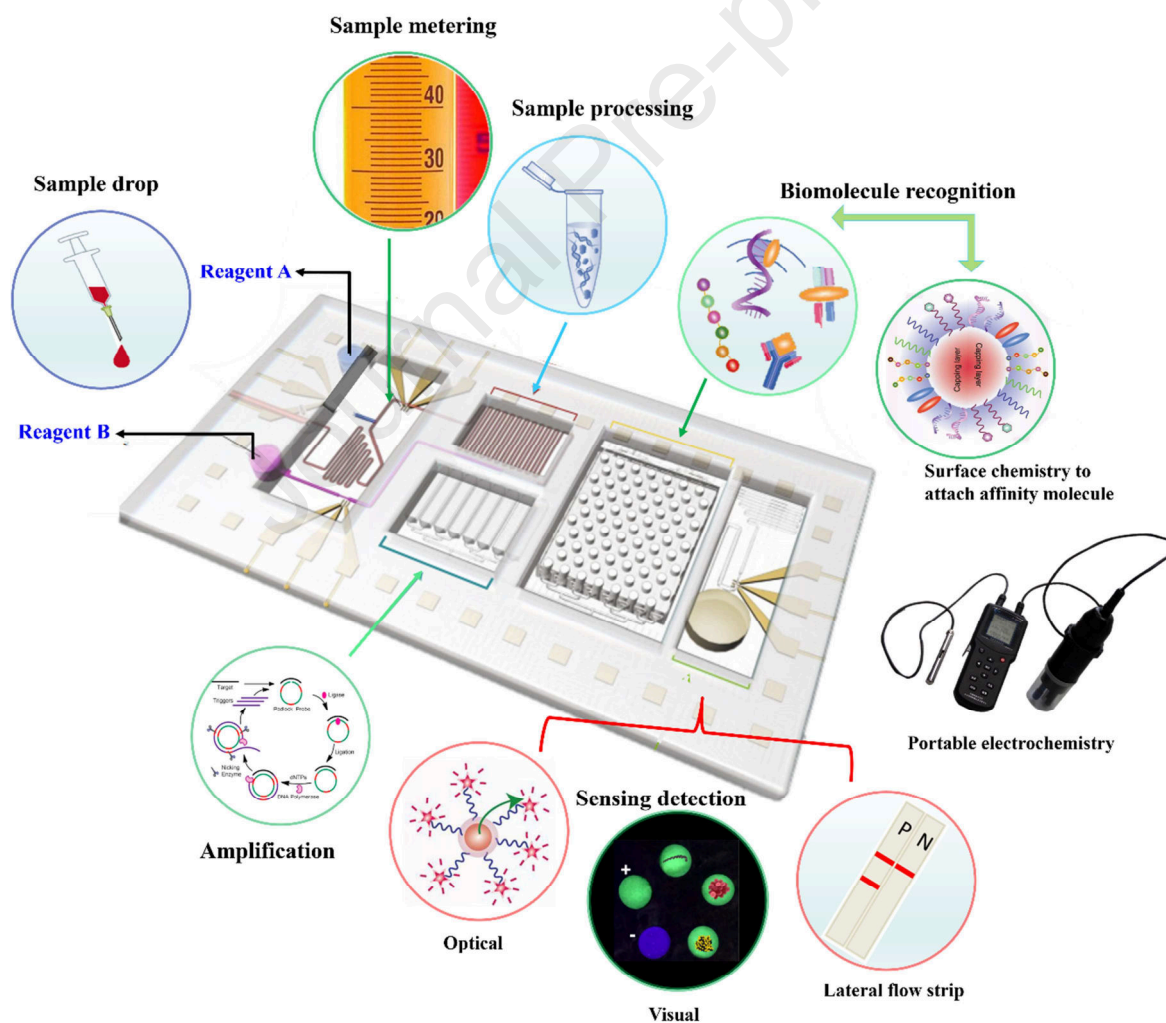
96

97 Fig. 1. The concept for an integrated POC biosensor for SARS-CoV-2 identification and COVID-19
98 biomarker quantification. A negative test is finished by adding the same channel and reaction cavity as the

99   sample test process (seen in Fig. S3).

100

101   An integrated biosensor has the potential to rapidly diagnose pathogens and efficiently monitor

102   infection transmission through self-tests performed outside the hospital. Device integration can

103   integrate all the steps of the biosensor into a small portable device, which is conducive to complex

104   real-time diagnosis (Kozel and Burnham-Marusich 2017). Recent advances in microfluidic

105   technology (including paper microfluidic device) and nanotechnology have brought us closer than

106   ever to the realization of simple yet highly sensitive and specific biosensors that can be used in

107   complicated environments without a central laboratory (Zhuang et al. 2020). Highly sensitive and

108   specific biosensors enable disease detection and diagnosis (Tab. S2). Fig. 1 shows the real-time

109   diagnostic biosensor concept for COVID-19 monitoring, which contains most of the elements needed

110   to measure all the above targets related to COVID-19 diagnosis. We also provide two typical

111   examples of fabrication and principles of related biosensors (nano-biosensor in Fig. S1 and integrated

112   biosensor in Fig. S2).

113   For example, we have recently developed a small paper-based analytical tool that can integrate all

114   the processes, including enrichment, extraction, purification, amplification, and visual detection for

115   nucleic acid testing (Yang et al. 2018). The whole process can be completed with the simple

116   folding-unfolding of the paper device without a power or pump supply, which can be used in limited

117   resource areas. In addition, during the COVID-19 pandemic, areas with local infectious disease

118   epidemics, such as Africa and the malaria epidemic (Reboud et al. 2019), have a high risk of

119   simultaneous outbreaks together with COVID-19. The biosensor also has the ability to rapidly and

120   accurately simultaneously identify and screen for COVID-19 and other local infectious diseases,

121   serving as an early warning system in resource-poor areas. For example, a paper-origami device has

122   been successfully employed to simultaneously diagnose two bovine bacteria and herpes virus-1 in

123   rural India (Yang et al. 2018).

124   There are also reports of the simultaneous detection of human viruses. Acute febrile diseases,

125   such as chikungunya and dengue, are related to the high burden of diseases in the tropics and have

126   many non-specific symptoms. In the absence of available laboratory diagnostic tools, it is difficult to

127   diagnose by routine examination alone. Wang et al (Wang et al. 2019) demonstrated a rapid analytical

128   method based on colour-mixing encoding and a readout strategy with the capability of performing

129   selective and sensitive multiplexed analyses of dengue and chikungunya in clinical samples within 30

130   min. Their multiplex assay could concurrently detect four targets using a low sample volume in a

131   resource-limited setting. These studies demonstrate that paper-based biosensors with the ability to

132   perform fast, precise and high-quality diagnostics enable multiplex, sensitive, and selective analysis

133   of infectious diseases and pathogens.

134   In resource-limited areas, health care services may be overwhelmed; therefore, it is important to

135   develop testing kits with the capability for self-detection. Biosensors provide an important

136   opportunity for family and community monitoring and have the potential to alleviate the current

137   dilemma. At the same time, the use of biosensors to quantify host immune biomarkers in patients will

138   aid in determining the severity of patients' symptoms, detecting the state of the host's immune system

139   and identifying organ disorders, and this information can be applied to strategically allocate resources

140   to optimize health care by adapting the classification process, the requirement for admission or

141   intensive care, and the administration of various treatments. The real-time diagnostic biosensor can

142   easily obtain timely information on pathogens and host responses in almost any location, and its

143   turnaround time is very fast. It can accurately identify potential patients, prompting corresponding

144 interventions. This has a profound impact on understanding disease characteristics and transmission

145 processes and guiding clinical treatment and health care, especially for infectious diseases (Bains

146 2014; Peacock and Weinstock 2014).

2.2. Community sewage sensors for tracing and early warning of COVID-19

148 Recently, it has been reported that the genetic material of SARS-CoV-2 has been detected in

149 sewage treatment plants in several countries, including France (Wurtzer et al. 2020), the Netherlands

150 (Medema et al. 2020), Australia (Ahmed et al. 2020), Italy (La Rosa et al. 2020), the USA (Nemudryi et

151 al. 2020; Wu et al. 2020), Spain (Randazzo et al. 2020), Turkey (Kocamemi et al. 2020), India (Arora et

152 al. 2020), China (Chen et al. 2020) and other countries (Haramoto et al. 2020; Mallapaty 2020). Hence,

153 the analysis of SARS-CoV-2 in raw sewage can trace the source of COVID-19 and determine whether

154 there are potential virus carriers in certain areas (Mao et al. 2020b). Furthermore, wastewater analysis

155 can also be used as a more effective approach to evaluate the extent of the COVID-19 spread in the

156 population rather than testing each individual, more importantly, the cost and rapidness are much

157 improved (Bhalla et al. 2020). Because the genetic material of viral RNA from people who have mild

158 or no symptoms will also enter the wastewater treatment plant, wastewater analysis methods can test

159 all people in the community. Murakami et al further performed wastewater analysis to overcome

160 representativeness and stigma issues related to COVID-19 (Murakami et al. 2020). Therefore, Bivins

161 et al further call for a global collaborative to maximize contributions of wastewater analysis in the

162 fight against COVID-19 (Bivins et al. 2020).

163 However, the current state-of-the-art analytical method for sewage involves sample enrichment,

164 and the detection still heavily depends on RT-qRCR, which needs a well-equipped laboratory and

165 well-trained personnel. Recently, much attention has been paid to sewage biosensors for monitoring

166 public health (Yang et al. 2015b). These sensors play a key role in the rapid analysis of pathogens and

167   other disease biomarkers in wastewater due to their excellent merits, such as rapid response, cost

168   effectiveness, and small sample requirements (Yang et al. 2017). Therefore, community sewage

169   biosensors can be used to collect timely information about COVID-19 for the whole community and

170   report results to health institutions, facilitating early prevention measures and effects (Fig. 2). If

171   SARS-CoV-2 can be detected in the local community at an early stage through a community sewage

172   biosensor, an effective intervention can be implemented in a real-time fashion, and restrictions on

173   SARS-CoV-2 transmission will minimize the spread of the disease and the threat to public health.

174   Potential patients will also benefit from the community sewage sensor tracing of SARS-CoV-2

175   sources, which will provide information for accurate and timely treatment.
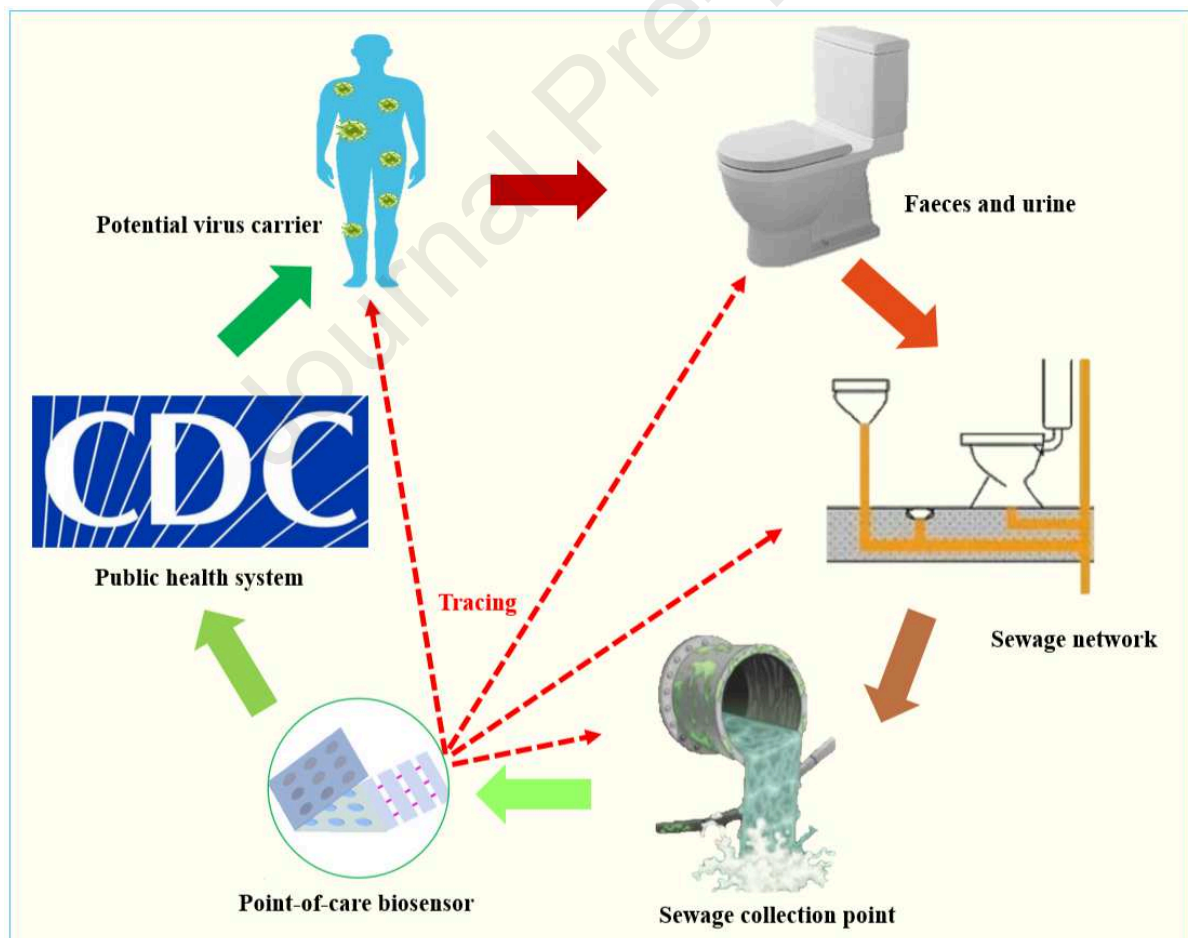
176
177   Fig. 2. The community sewage biosensor for tracing COVID-19 sources and implementing effective
178   interventions.
179

2.3. Biosensor-based mHealth for health care and epidemic management for effective intervention

Mobile health (mHealth)-based biosensors have great potential to overcome the limitations of a shortage of medical resources and alleviate this dilemma to facilitate effective intervention. mHealth is the application of mobile devices, components, and related technologies in the field of health care. mHealth provides an ideal framework for real-time and effective health care and epidemic management, which is achieved through targeted behavioural changes (through interactive applications), care roadmaps (based in the community or the clinic), and monitoring by connected diagnosis. mHealth technology improves the speed, efficiency, and appropriateness of the comprehensive public health and clinical response to the epidemic mainly through two mechanisms: increased access to health care outside the clinical environment (such as self-testing) and reporting of the diagnostic results to medical professionals and public health departments in (nearly) real-time to identify an epidemic outbreak in an area, thus ensuring efficient clinical and public health responses. Patients report their self-test results to the hospital and public health management department through the mobile health system; then, the hospital puts forward diagnosis and treatment suggestions depending on the patient's actual situation (Fig. 3).

The implementation of these mechanisms involves the fast transmission and storage of data as well as the connection of all related parties, all of which require a sufficient hardware foundation and technical support. The rapid development of portable communication technology, such as 5G, and digital computing, such as the concepts of "big data" and "blockchain", improves the speed and efficiency of data processing and exchange. Additionally, the widespread use of smartphones and the networks needed to support them reduce data collection and transmission costs. This powerful handheld computer with sensors/biosensors and wireless connections provides scientists and medical

203 systems with the possibility of capturing and processing data (Perkel 2017). Regardless of whether a

204 setting has abundant or limited resources, the application scope and capability of smartphones and

205 their related technologies are increasing. Currently, these smartphones offer low-cost sensing and

206 processing capabilities comparable to expensive "high-end" devices. In addition, the mHealth system

207 can also promote efficiency by improving the automation of inventory and supply chain management

208 systems, reducing the workload and errors related to paper reports, and preventing materials from

209 running out (Namisango et al. 2016).
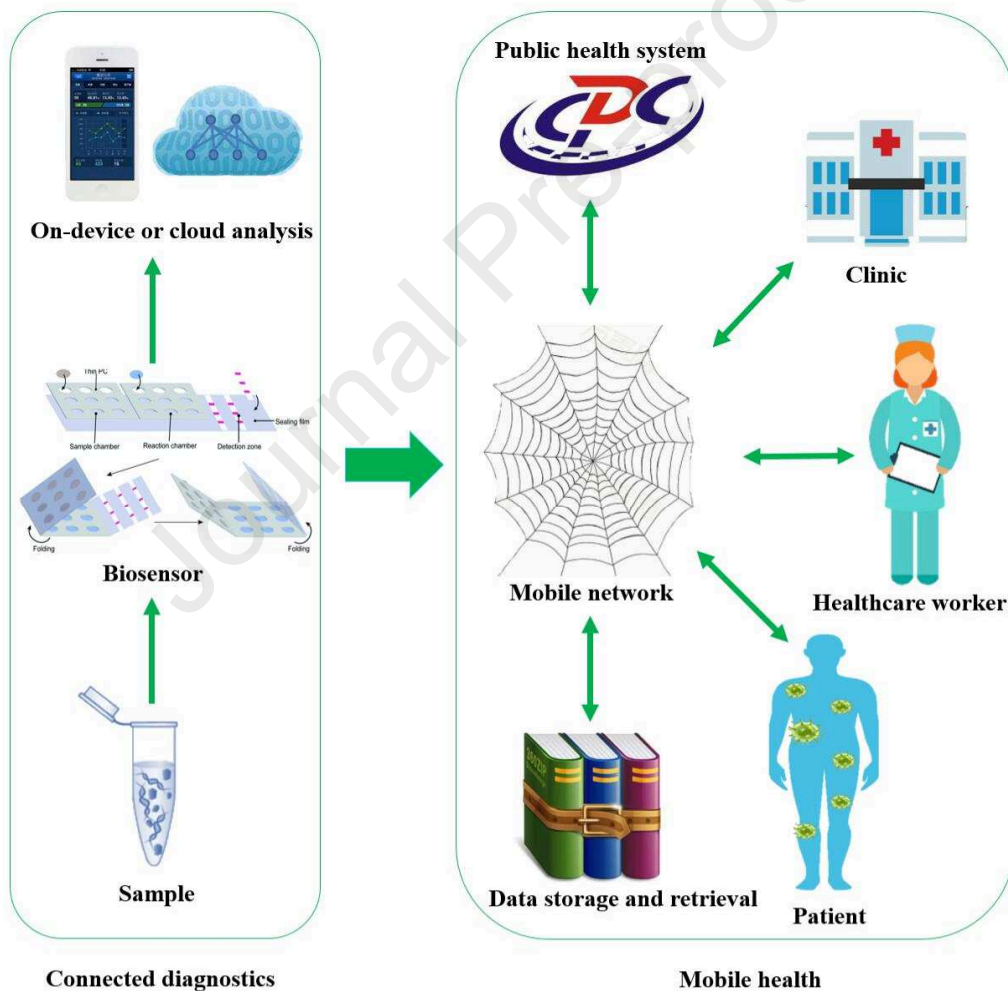
210

211 Fig. 3. POC biosensor-based mHealth system. The stages, stakeholders, and possible outcomes of
212 deploying an effective mHealth intervention that uses a connected biosensor.

213

214   mHealth has been proven to be useful for internet-based clinical and public health responses to

215   some infectious diseases. In a study from the United Kingdom, a comprehensive online prevention,

216   diagnosis, and health care plan was presented (Estcourt et al. 2017). Chlamydia-infected patients were

217   managed by online clinical consultations; the patients received a link to access their clinical records

218   and even obtain antibiotics from pharmacies. The system also integrated partner notifications, health

219   promotion and automated monitoring data collection to help prevent the spread of this potentially

220   asymptomatic sexually transmitted infectious disease.

221   A biosensor can be a simple (a self-test), fast (real-time or nearly real-time) diagnosis method or

222   detection technology to determine the relevant diagnostic target of an infectious disease (Bissonnette

223   and Bergeron 2017) and automatically transmit the diagnosis results to the mHealth system, which

224   will greatly speed up the patient's access to treatment and consultation. COVID-19 detection and the

225   application of the online diagnostic and symptom reporting application combined with a standardized

226   epidemiological and clinical data collection have a substantial opportunity to improve the speed and

227   efficiency of monitoring and management of the epidemic (Fallah et al. 2017). The rapid results

228   acquired by POC biosensors can be monitored through geospatial maps utilizing geographical

229   markers (Chunara et al. 2012) or by social network and internet search analyses, which provide an

230   integration tool that can be applied to epidemic control (Lampos et al. 2015; Yom-Tov et al. 2015).

231   COVID-19 can be detected and treated rapidly with mobile surveillance, and the real-time monitoring

232   of epidemic areas can be intensified (Hayward et al. 2014). Moreover, the public health department

233   can monitor the epidemic with the real-time mHealth system and take appropriate measures, such as

234   regional isolation and the allocation of strategic materials. All participants in the mobile system,

235   including potential patients, medical staff and public health departments, can quickly understand the

236   mobile health system, which can facilitate the diagnosis and treatment of potential patients. Medical

237   staff can better guide patients' health care, and public health departments can better monitor the

238   epidemic and implement interventions such as the timely isolation of confirmed patients, protection of

239   healthy people, and allocation of public resources. Mobile systems, in combination with

240   internet-connected diagnostic biosensors, provide new methods for the diagnosis, tracking, and

241   control of infectious diseases while improving the efficiency of the health system (Fig. 3).

242   In addition, microfluidics sensing technology for effective drug screening and delivery holds the

243   potential for therapy of SARS-CoV-2. Microfluidic chips afford considerable advantages in drug

244   release, such as precise and multi-dosing release, targeted precise release, sustainable control of

245   delivery, and small side effects, etc., which are important assets for drug delivery systems (see Part

246   S3). Microfluidic technology has been gradually applied to the preparation of drug carriers, direct

247   drug delivery systems, drug preparation and fixation. Inexpensive and easily manufactured materials

248   are rich substrates that naturally integrate multiple functions, which include filtration, storage,

249   transport, valves, multiplexing, and concentration. Microfluidics has great potential to be used in the

250   research of COVID-19 therapies to avoid ineffectiveness and health risks.

251   **3.   Conclusions and perspectives**

252   Effective prevention, monitoring, and interventions are important for slowing the spread of the

253   disease and reducing the prevalence of COVID-19. We have proposed to use iBMW to provide an

254   ideal framework to manage pandemics, from the perspectives of prevention, detection and

255   intervention. The innovative miniaturization and portability of community sewage biosensors provide

256   the possibility to trace potential sources in the field, and iBMW can directly identify pathogens and

257   provide required biomarker data in a short period of time through self-testing. The real-time data

258   collected and transmitted by the iBMW not only provide timely health care and treatment for patients

259   but also allow for the timely implementation of epidemic control measures. COVID-19 can be

260   accurately controlled by public health prevention measures according to the epidemic situation in

261   different regions. Considering this timely information regarding the SARS-CoV-2 infection status and

262   host reactions, the mHealth system can be used to monitor and control the epidemic. Hence, the use of

263   iBMW could reduce the time from the onset of infection to the appropriate therapeutics. In addition,

264   the fast growth of microfluidic sensing technology has provided new opportunities for effective drug

265   screening and drug release in in vitro tests, which will be beneficial for the development of effective

266   therapeutic drugs and vaccines without a safety risk.

267   Although it still remains some challenges of biosensors for COVID-19 remain (listed in Tab. S3),

268   the application of biosensors provides a systematic approach for alleviating the current dilemma

269   associated with the prevention, monitoring and intervention of COVID-19. In particular, biosensors

270   can trace potential virus carriers early, rapidly confirm suspected cases with self-tests, increase the

271   chance of patients obtaining precise medical treatment, decrease the risk of medical staff infection,

272   monitor and manage the pandemic in real time, support therapeutic drug screening and drug delivery

273   systems, and finally control the epidemic through timely response.

274   **Acknowledgements**

278   **Notes**

279   The authors declare no competing financial interest.

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Highlights

- Point-of-care biosensors for rapid and reliable COVID-19 diagnosis
- Community sewage sensors for tracing and early warning of COVID-19 within population
- Point-of-use sensor-based mHealth for health care and epidemic management and intervention
- Microfluidics for effective drug delivery for potential therapy of COVID-19

The authors declare no competing financial interest.