Point-of-care diagnosis of COVID-19 at IHU Méditerranée Infection, Marseille, France.

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ABSTRACT

In order to face the wave of COVID-19 diagnosis by RT-PCR, the IHU Méditerranée Infection deployed point-of-care laboratories to complement ~~to~~ the core-laboratory. We upgraded previously implanted POC by extending their position close to patients and doctors in emergency rooms, adapting instruments and protocols to speed up diagnosis, and ensuring sampling and manipulations to limit contamination of operators and samples. From April to November 2020, 31,087 RT-PCR tests have been performed in POCs for 25,336 different patients; with an overall positivity of 19.5% with a mean delay of the result of 1h26min +/- 23 min. In particular, deploying protected cabins with last generation thermocyclers proved effective in limiting environmental contamination by the viral RNA, preventing contamination of operator and while providing results within 01h02min +/- 6 min. The experience reported here with rapid POC diagnosis of COVID-19 could be worth transposition into similar massive epidemic situations and regular microbiological surveys of at-risk populations.

INTRODUCTION

The brutal and massive Coronavirus Disease 2019 (COVID-19) pandemic due to the SARS-CoV-2 coronavirus [1] has questioned the routine organization of diagnostic laboratories worldwide, giving an opportunity to think about new laboratory organizations in order to cope with the contradictory needs of massive detection, massive diagnosis and shortened delay of detection of the coronavirus [2]; applying the basic hygiene rules of the laboratory [3, 4]. The centralized approach of COVID-19 laboratory diagnosis consisting in multi-site sampling followed by tests in the core laboratory, delays diagnosis in selected populations such as the elderly people who need a rapid diagnosis and treatment to being more susceptible to developing severe and deadly infections [5]; and delay the traceability of contact persons and travelers to limit outbreaks in selected communities. The point-of-care (POC) diagnosis may offer an alternative to practice reverse-transcription polymerase chain reaction (RT-PCR) detection of viral RNA in nasopharyngeal swabs and other samples. In order to face these challenges, we developed a point-of-care (POC) approach complementary to the upgrade of core-laboratory [6]; in the dual perspective of diagnosing populations who do not have an easy access to core-laboratory and speeding the diagnosis in these populations. We invented a mobile COVID-19 mini-laboratory with a screening system combining sampling, testing, recording and sending the results of tests. This inclusive solution wui an inflatable cabin including a secured sampling module; a biosafety cabinet for safe sample handling and RT-PCR devices to perform molecular tests in a half hour with less than 5 minutes hands-on time; test results are recorded and sent to patients using a computer equipped with medical biobank software. We adapted the

POC laboratories we had previously implanted in our tertiary university hospitals [7, 8] by extending their locations, upgrading instruments and protocols and securitizing sampling and manipulations of the samples.

The POC had to be modulated to face the unique challenges of the COVID-19 epidemics, in the IHU Méditerranée Infection, Marseille, France. We are presenting our unique experience in POC diagnosis of COVID-19.

PRE-COVID-19 POCs IN THE IHU. The concept and practice of POC laboratories was born in 2008 when the microbiology laboratory had to move from the North Hospital to the Timone Hospital, distant 14 kilometers away and 20-30 minutes driving [8]. In order to provide doctors with rapid diagnosis of some infectious diseases, we implanted the first POC laboratory within the Adult Emergency Room in North Hospital; and rapidly duplicated it within the Timone Hospital. At that time, POC laboratories were operated by residents in biology with a background in medicine or pharmacy under the supervision of the three heads of laboratory. These POCs basically used syndromic kits in order to detect as quickly as possible pathogens responsible for deadly infections as well as most frequent pathogens regardless of the potential severity. Since October 2020, the IHU Méditerranée Infection is operating four POC laboratories (Figure 1) devoted to COVID-19 diagnosis and medical management, instead of two POC laboratories in the pre-COVID-19 period, in January 2020. All these four POCs were operated under the responsibility and supervision of the three heads of the core-laboratory. Upgrading COVID-19 POCs included improving professional and instrumental skills, extending POC locations and securitizing sampling and sample handling in the POC. The overall management of POC scale-up along the COVID-19 story in IHU Méditerranée Infection was done through one daily general strategic meeting followed by one daily technical meeting. All the POCs performing RT-PCR tests were connected to the informatic system of the core- laboratory and the one of the public university hospitals in Marseille (Assistance Publique- Hôpitaux de Marseille).

UPGRADING POCs. ~~In order~~ To cope with the wave of COVID-19 tests, we had to increase the capabilities of POC laboratories in three directions: (1) geographic extension of POC locations in and out of the IHU building (2), update equipment of POCs (3) extend training to new categories of personnel.

From two POC laboratories in the pre-COVID-19 period, the IHU operated four POC laboratories during the COVID-19 period: the IHU opened one new POC laboratory in the Adult Emergency Department of Timone Hospital and new one POC laboratory into the hall of the IHU building, the latter formed by two deployable POC check-points (POCRAMé, Marseille, France) performing 4 thermocyclers each for ~~a~~ capacity of 150 RT-PCR tests per day. Later check-point, the last one dispositive, was thoroughly investigated during the COVID-19 epidemics. These four POCs were equipped with new generation thermocyclers for RT-PCR (VitaPCR®, bioSynex, Credo diagnostics, Singapore) measuring 16.5 cm wide, 20.5 cm deep and 15.5 mm high, 1.2 kg to perform molecular tests as previously described [9]. In details, the POC operator was stirring each nasopharyngeal swab 15 times in the collection buffer for viruses lysis and inactivation (bioSynex, Credo diagnostics) and 30 µL of the lysate were transferred in a tube containing the lyophilized PCR-reagents and well-mixed (20 times) by pipetting using an electronic pipette (Mettler Toledo, Greifensee, Switzerland) in order to limit the formation of bubbles. The tube was then introduced in the thermocycler and RT-PCR results were provided in 20 minutes. The Vita PCR assay included three detection systems: the first detection target was a sequence located in the human beta-globin gene, used as a sample adequacy control (SAC) to ensure adequate addition of sample and monitoring the presence of inhibition factors in the PCR process; the second one was a specific sequence to SARS-CoV-2 located in the nucleocapsid (N) gene named (SARS-CoV-2); the third detection target was a conserved sequence common to SARS-CoV-2, SARS-CoV and SARS-like bat coronavirus, also located on the N gene named SARS-like. Accordingly, four results were possible: an “invalid result” meaning that the SAC was not detected, a “negative result” meaning that the SAC was detected but not the other targets, a “positive result” when the SAC was detected with SARS-CoV-2 alone or with SARS-CoV-2 and SARS-like and a “presumptive positive result” when the SAC was detected with SARS-like target. Test result was then entered in the NexLabs medical software and the patient received instantly the result by login in the website of Assistance Publique-Hôpitaux de Marseille (APHM) using his personal username.

Furthermore, we extended staff assigned by residents in biology in the pre-COVID-19 period, to undergraduate students in pharmacy and laboratory technicians during the COVID-19 period. Initial training of undergraduate students, who had previously never used the secured cabin and the RT-PCR system, was carried out by one of us (AB) in two hours with groups of 4 students each. The training was divided into three stages, namely 1): how to obtain a nasopharyngeal swab specimen inside the confined cabin (30 min); 2) how to run an RT-PCR test using the VITA-PCR device (1H30); 3) how to record the PCR results with NexLab medical software (30 min).

CHECK-POINT POCs. We deployed two secured check-points featuring a 30-kg, 4.14 square-meters polyvinyl chloride cabin (MEPHIPOINT®, POCRAME, Marseille, France) for the POC diagnosis of COVID-19 at the IHU Méditerranée Infection (Supplementary figure 1). This cabin, inflatable in 5 minutes using an electric air pump, is equipped with gloves directed outwards to secure sampling and avoid the exposure of staff to infected patients when collecting nasopharyngeal swab. The cabin is completely airtight with a zippered door and an air exchanger equipped with high-efficiency particulate air (HEPA) filters protecting the environment from any contamination that may come from inside the cabin and protect users from any contamination that may come outside. The deployment of the confined cabin was done by two trained people in 30 +/- 10 minutes and inflates had to be refilled after 24 hours. The cabin included a biosafety cabinet MEPHILAB® (POCRAMé) 65 cm (W), 160 cm (H), 60 cm (P) for safe sample handling, as previously described [10]; four thermocyclers for RT-PCR (VitaPCR®) as described above; and a computer with medical software (NexLabs, Technidata, Montbonnot-Saint-Martin, France) for test results recording and sending to patients (Supplementary Fig. 1). The operator could subsequently sampled four patients successively by collecting a nasopharyngeal swab using the integrated gloves; stirring each swab 15 times in the collection buffer for viruses lysis and inactivation; throwing the swab into dedicated trash and introducing the collection buffer tube inside the cabin through a through-wall decontamination device containing a decontamination solution to eliminate any

DNA/RNA contamination on the surface of collection buffer tube before running four RT-PCR tests in parallel (one test per thermocycler), as previously described [9] (Supplementary Video). To check the efficiency of the through-wall decontamination device to prevent RNA contaminations, samples were taken from different points of the secured cabins. Seven samples were taken from 1) the upper part of the gloves, 2) the lower part of the gloves, 3) the worktop of MEPHILAB®, 4) and 5) the surfaces of two Vita-PCR thermocyclers, 7) the computer keyboard used for recording results. SARS-CoV-2 RNA was tentatively amplified using the VITA-PCR system in the presence of two negative controls. The results showed detection of the “SAC” targeting the human beta-globin in the six different points but no SARS-CoV-2 detection was recorded. Also, “SARS-like” sequence was detected in the upper part of the gloves (Ct 35), in the surface of vita-PCR (Ct) and in the computer keyboard (Supplementary Table 1). These observations prompted to ask operators to decontaminate gloves between sample preparation, handling of the thermocyclers and using the keyboard of the computer. The cabin was operated for 6 weeks by pharmacy students enrolled on a voluntary basis as part of their associative activities within the Association of Students in Pharmacy of Provence. Student training (see above) efficiency was measured by seven participants as using the flow for each step of the process (sampling, PCR handling and recording results), as proxies. A total of 178 measures indicated that the average sampling time was 2 min 31 s, 2 min 59 s for PCR handling and 45 s for recording results (Supplementary Table 2). Over a six-weeks period (from August 24, 2020 to October 2, 2020), 3,568 / 3,643 (98%) tests retrospectively analyzed in this study, have been validated by the detection of the sample adequacy control (SAC), including 2,010

(56.%) negative tests, 1,281 (35.90%) positive tests and 277 (7.76%) presumptive positive tests. The flow rate for one secured cabin including four RT-PCR machines was calculated as 8-10 tests per hour including sampling, RT-PCR tests and recording the results. Test results were returned within 30 min. All positive cases were invited for follow up care at the IHU Méditerranée Infection.

CONCLUSIONS

Large-scale testing for SARS-CoV-2 has been successfully conducted in countries such as South Korea and Singapore leading to flatten the curve of the disease through massive testing including setting up drive-through testing stations and then isolation of infected individuals [11]. In particular, many drive-through satellites were used during COVID-19 pandemic to collect large volume of samples [12, 13] to perform RT-PCR tests in centralized laboratories. The data here reported indicate that complementarity POC dispositive proved efficient to cope with a huge epidemic at different levels of proximity with patients. In our experience, a total of 31,087 RT-PCR tests have been performed in 25,336 different patients with an overall positivity rate of 19.52% (Figure 2); with a median delay of 1h26min +/- 23 min (Supplementary figure 2-4 and supplementary table 3)

In complement, a deployable secured check-point equipped with last generation thermocyclers proved efficient in safely deliver accurate detection of the SARS-CoV-2 within one hour. The RT-PCR tool used in secured cabins required less than 5 min of hands-on time preparation with minimal training. The results were available in 20 minutes and the interpretation was fully-automatic. PCR reagents are stored at room temperature facilitating the deployment of the device in isolated areas. This simple method could be easily deployed to field locations where central laboratories do not exist and COVID-19 testing is greatly needed. As an example, we deployed the MEPHIPOINT on-board a commercial cruise ship for the rapid screening of the ship's crew and were able to test 39 persons within 6.5 hours, from the on-board arrival until leaving the ship.

We propose that the strategic implementation of portable and mobile mini-laboratories would allow to secure the rapid diagnosis of COVID-19 at the points of care, allowing to combine the two approaches and reposition RT-PCR test using POC tools towards populations which are far from central laboratories such as rural areas, isolated professional categories such as sailors to identify cases rapidly and initiate early treatment and appropriate isolation measures.

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CONFLICTS OF INTERESTS.

AB is an employee of POCRAMé, which MEPHIPOINT product is reported in this work.

DR, PYL and MD are co-founders and shareholders of POCRAMé.

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Figure Legends

Figure 1. POCs performing SARS-CoV2 tests managed by IHU Méditerranée Infection, Marseille, France.

Figure 2. Number of SARS-CoV2 tests performed in POCs and positive results ratio.

Figure 3. SARS-CoV2 RT-PCR tests performed in POCs among the totality of RT-PCR tests performed in the IHU Méditerranée Infection.

Supplementary Data

Supplementary Table 1. Contamination testing results for a secured cabin: Surface sampling of check-point disposal.

Supplementary table 2. Measures of sampling, handling and results recording in check-point disposal.

Supplementary table 3. Mean and average deviation of POC tests duration

Supplementary figure 1. Check-point disposal composed of confined cabin MEPHIPOINT, biosafety cabinet MEPHILAB and RT-PCR devices Vita PCR.

Supplementary figure 2. Number of SARS-CoV2 tests performed with GenXpert along with delays of tests

Supplementary figure 3. Number of SARS-CoV2 tests performed with Biofire FilmArray along with delays of tests

Supplementary figure 4. Number of SARS-CoV2 tests performed with Vita PCR along with delays of tests.