New Institute to fight threats: the COVID-19 paradigm.

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ABSTRACT: The Hospital-University Institute (IHU) Méditerranée Infection features a 27,000 square meter building hosting 700 employees and 75 hospitalized patients in the center of Marseille, France. We report that previous preparedness in contagious disease management allowed the IHU to manage the COVID-19 outbreak by continuing adaptation for optimal diagnosis, care and outcome for more than 14,000 patients, providing the opportunity for 155 publications and 132 videos posted on the IHU Facebook network, totaling 41.5 million views and 301,000 followers, and dealing with COVID-19, outbreaks, epistemology, and ethics in medicine.

The very first case of COVID-19 in Marseille was diagnosed in the IHU Méditerranée Infection (IHU) in Marseille, France on February 27, 2020, and the IHU had to continuously adapt its strategy over 9 months of the epidemic in Marseille to cope with the overwhelming waves of COVID-19, later proved to be caused by at least three different lineages of SARS-CoV-2 [1] [Fournier P.-E. et al., in this CID issue]. We here review the key steps in this adaptation, while point-of-care (POC) laboratories will be presented in another chapter [Bouam A. et al., in this CID issue].

The IHU Méditerranée Infection: built to confront epidemics.

The IHU Méditerranée Infection (herein designated as IHU), held by a foundation called Fondation Méditerranée Infection, whose overall structure and functional organigram are presented in supplementary data, was created in 2011 as part of the program Investissements d'Avenir launched by the French government, and was the only such institute devoted to infectious and tropical diseases [2] [3]. While the IHU is conveniently located in the university hospital medical campus in the heart of Marseille, it primarily serves the population of the Marseille area and Provence at large, acting as the National Reference Center for infectious diseases, hosting patients from all over France and abroad. As a private law regime foundation, the IHU has great agility in decision-making, which has been a key point in effectively confronting the COVID-19 outbreak. All strategic decisions could be validated in a weekly Director Committee meeting, decisions being immediately enforced.

The IHU is a 27,000 square meter building conceived to accommodate contagious patients and potentially hazardous samples even in the case of epidemics, consisting of four horizontal lobbies squared into three vertical sectors consisting of a university hospital sector, a laboratory sector and a tertiary sector; the overall building is under strict access control, including biometric access control in some of the more critical sectors (Figure 1) (https://www.mediterranee-infection.com/en/). The project consisted in building *ex nihilo* on the Marseille Medical Timone Campus a research hospital specifically dedicated to infectious diseases and securely protected to care for contagious patients, with a formidably equipped diagnostic microbiology laboratory capable of containing extremely contagious pathogens, including potential agents of bioterrorism, in a 1,200 square meter biosafety level 3 (BSL3) laboratory. There are four research units, as well as startups and spinoffs benefiting from IHU know-how and developments in the field of infectious disease. For patient care, three wards of 25 single rooms consisting of: one ward for acute emergency infectious diseases, one ward for chronic infections and one ward dedicated to contagious diseases equipped for biosafety level 3, with 3 modules of 7, 8 and 10 beds. Module A (7 beds) is pre-equipped for intensive care, and every room is accordingly remotely controlled. A BSL3 point-of-care (POC) laboratory is located within the ward for diagnostic and routine laboratory tests for contagious patients, under the supervision of the microbiology team. Visitors are not admitted to the unit and patient visits must be accessed via an external corridor, if allowed [4]. The outpatient clinic on the first floor includes a 21-bed day hospital and a specific and dedicated area for rapid diagnostic screening, avoiding encounters between contagious patients and other patients and personnel in the

institute [4]. All care facilities can be depressurized. Heath care personnel are regularly trained, based on monthly exercises and by regular real-life practice, as was the case with patients returning from Saudi Arabia and suspected of MERS-Cov [5], and they benefit from a specific medical program of vaccination-based protection against infectious diseases and serological monitoring on a voluntary basis.

In close connection with the research hospital sector, the Microbiology Laboratory of the IHU consists of POC laboratories, presented in an additional paper [Bouam A et al., in this CID issue], and a large, 2,341 square meter diagnostic core laboratory organized in platforms: a reception platform entering information in the laboratory informatics system, dispatching clinical sample aliquots on the technical platforms and preparing biobanking; a culture platform; a molecular biology platform performing nucleic acid extraction and PCR-based tests; a serology platform performing enzyme-linked immunosorbent assays (ELISAs), indirect immunofluorescence assays and automated Western-immunoblotting assays; and a large secured biobank with a storage capacity of 1 million samples at -80°C and 2 million samples at -20°C for preservation of clinical samples, isolates and nucleic acid extracts. All platforms are informatically interconnected (on-going) and informatically connected to the information system of the public university hospitals in Marseille (Assistance Publique à Marseille). In fact, platform equipment has been regularly updated in order to be permanently equipped with the most efficient, advanced diagnostic techniques. For direct examination of samples, the IHU laboratory is equipped with the latest generation electron microscopes (TM4000plus scanning electron microscope, Hitachi, Tokyo, Japan) which combine the power of traditional electron microscopes with the ease of

optical microscopes, rendering electron microscopy a routine technique for the observation of samples and microbes [6]. The culture platform is equipped with the largest worldwide capacity for matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF), with 8 MALDI-TOF instruments and a unique spectrum database to identify microorganisms and pathogens [7] and their potential vectors [8]. The molecular biology platform comprises 28 thermocyclers, while downstream routine sequencing was launched in 1992, after the IHU ancestor bought the first automatic sequencer in Europe. The sequencing platform is now equipped with 4 MiSeq instruments (Illumina, Paris, France), 2 Gridion and 1 PromethION instruments (Oxford Nanopore, Oxford, UK), as well as 1 iSeq (Illumina) and 4 MiNion instruments (Oxford Nanopore), more specifically dedicated to POC applications. In addition, a 1,200 square meter NSB3 security laboratory with biometric access control allows for isolation, culture, manipulation and testing and storage of contagious pathogens [9]. These platforms, dedicated to the routine diagnosis of infectious and tropical diseases, are routinely served by 215 qualified personnel, including 29 certified biologists, 24 engineers and 21 residents in medical biology. All these resources have been mobilized to fight the COVID-19 epidemic in France.

IHU fighting the COVID-19 epidemic

As early as January 31, 2020, Europeans repatriated from Wuhan, placed in provisional quarantine 20 kilometers from the IHU, were evaluated by the IHU, following its capability in developing RT-PCR testing from scratch before any diagnostic test was commercially available. Internal expertise was mobilized in primer design, based on

SARS-CoV-2 viral sequence analysis and experimental protocol design, so that testing capability reached 500 tests/day for the diagnosis and follow-up during the quarantine of those repatriated [10]. A daily COVID-19 steering committee met as early as January 31 and continued as such for precise day-by-day management of the outbreak.

Accordingly, we developed a rapid virological screening circuit, so that RT-PCR results were available within 3 hours of laboratory management [11]. This organization plan was set up very early, just as we diagnosed the first positive patient, and was adapted throughout the outbreak to respond to changing situations, creating five different COVID-19 laboratory circuits: (1) a POC circuit, including an innovative check-point as detailed in [12] [Bouam A et al., in this CID issue]; (2) a hospitalized-patient circuit, with the goal of obtaining RT-PCR results before 10 AM in order to manage hospitalization turnover; (3) an emergency circuit, with the goal of delivering RT-PCR results within 4 hours; (4) a routine circuit, with the goal of delivering RT-PCR results within 8 hours; (5) and an external sample circuit, with the goal of delivering RT-PCR results within 24 hours. In order to achieve these goals, we progressively increased the capacity for obtaining nasopharyngeal samples by ultimately creating five posts, using the national SI-DEP system, served by a pool of 14 recruited personnel. Also, core laboratory facilities were extended to three additional laboratory rooms previously devoted to research activities, adding 184 square meters of laboratory where additional instruments were installed: the Molecular Biology platform had an increase of four nucleic acid extractors for a total of 20 extractors, one RT-PCR thermocycler for a total of 19 thermocyclers, and was equipped with two plaque preparators that were not available before the COVID-19 epidemic. In addition, we added 6 informatics posts.

More than 460,000 RT-PCR custom-made tests have been fabricated in the IHU. In parallel, the activity of the Biosafety Safety Level 3 laboratory was redirected towards the high throughput isolation and culture of SARS-CoV-2 strains, the majority from nasopharyngeal swabs used in parallel for RT-PCR diagnosis [13]. This activity was rapidly crucial in determining a cut-off value for the accurate interpretation of RT-PCR cycle threshold (CT) after we showed that a CT value of > 34 allowed only 1% viable viruses [14]. Further, continuous high throughput isolation of SARS-CoV-2 strains proved determinant for *in cellulo* testing of the activity of different drugs, chiefly hydroxychloroquine, azithromycin and zinc [15–17] and the observation of SARS-CoV-2 strains exhibiting decreased *in cellulo* susceptibility [La Scola B. et al., in this CID issue]. Finally, SARS-CoV-2 culturing supported monitoring of partial and entire whole genome sequences to determine the various SARS-CoV-2 genotypes underlying the dynamics of COVID-19 epidemics, including the geographical sources, and provided antigens for the home-made serological tests, including indirect immunofluorescence and automated Western immunoblotting. In fact, the IHU developed from scratch SARS-CoV-2 serology based on indirect immunofluorescence before any serology test was commercially available [18]. Building such a test from scratch was made possible thanks to previous expertise acquired over the years in that technique, previously applied, among other applications, to facultative intracellular pathogens [19]. Conversely, setting-up indirect immunofluorescence SARS-CoV-2 serology provided the opportunity to automatize basically manual indirect immunofluorescence, by automatization of antigen spotting on slides (Echo 525, Labcyte, Beckman Coulter, Indianapolis, USA) and automation of slide reading using an automated fluorescent slide scanner (AxioScan Z1., Zeiss, Marly

le Roi, France). All the different commercially available serology techniques were progressively adopted, including POC lateral flow assays [20], enzyme-linked immunosorbent assays (ELISA) and chemiluminescence assays [20]. In order to support the routine medical care of COVID-19 patients, the laboratory increased its capacity for hydroxychloroquine assays by liquid chromatography (LC-UV) and implemented from scratch azithromycin assays by liquid chromatography-mass spectrometry (LC-MS) (Chabrière E. et al., unpublished data). Also, zinc assays were monitored and the total lymphocyte count, differential CD4/CD8 and NK counts were also routinely monitored, using flow cytometry (Aquios Tetra, Beckman Coulter). Altogether, a total of 58 different personnel were recruited specifically to deal with the additional laboratory activity, including 44 laboratory technicians and 14 secretaries, a 27% increase in laboratory personnel.

For patient care, the building was separated in three parts: one dedicated to patient screening, one for ambulatory care and one for hospitalization, including 25 single rooms in biosafety level 3 and 50 single rooms in uncontrolled air depression as cited above. We first used the 25 contagion rooms of the dedicated BSL3 ward, which gave us time to reorganize the other two wards. This time was also precious for our university hospital (AP-HM), as it provided three additional weeks to organize the surge capacity for the care of COVID patients concentrated in our institute during this time. Once the 75 beds were full, we organized the turnover of contagious patients (see below). Because symptomatic people were more likely to be PCR positive, the screening circuits were organized in two: symptomatic and asymptomatic people were

separated (Figure 1). The continuously rising number of people that came for testing during the first wave (peak of 3596 tests on April 3, 2020) and the prolonged waiting time in the line (up to 3 hours), with people arguing, became a true problem, and led us to set up a specific COVID 19 testing plan from 7:00 AM/7:00 PM, 6/7 days by individual appointment using the commercially available French web application “Doctolib,” or without appointment in dedicated time slots. This organization was so effective that we were able to test a thousand people per day without further trouble. Nasopharyngeal sampling was carried out by trained nurses and the samples were transferred immediately to the laboratory. Patient registration, presentation (symptomatic or not), and PCR results, ratio of infected/uninfected and ratio of positive in symptomatic and asymptomatic individuals was available in real time, 24/24H 7/7, on a dedicated screen and was used to monitor the epidemic. The standard turnaround time for PCR test results was 8 hours for routine diagnosis and 3 hours for the ICU and emergency department. We automatically sent all positive patients a brief text message, asking them if they wished to volunteer to be treated and followed in our center. All positive PCR tests performed elsewhere than the IHU where subject to control, with an ultra-short PCR testing turnaround available in 20 minutes, before enrolling the patient for care, which is reported in more detail in this issue [Bouam A. et al., in this CID issue].

The day hospital was organized to screen patients by nurses, with monitoring of vital signs, including pulse oximetry and laboratory investigation (D-dimers, C-reactive protein, fibrinogen, white blood cells and eosinophils), and an electrocardiogram was performed in all patients; abnormal EKGs were remotely monitored by the cardiology department. The day hospital was organized to screen ambulatory patients. The vital

signs, including pulse-oximetry and laboratory investigation (D-Dimers, C reactive Protein, fibrinogen, WBC and eosinophils) were carried out by nurses, electrocardiogram was performed to all patients and abnormal ones were controlled by tele consultation with the department of cardiology. Serum potassium levels were obtained in real time at the point of care (i-STAT ALINITY, Abbott Point of Care Inc.) to eliminate delays in treatment with HCQ and AZT. A low-dose CT lung scan was systematically carried out in patients older than 55 and/or with comorbidities and/or lung abnormalities on clinical examination and/or a SaO2 < 95%. The low-dose CT scans were conducted in the radiology department [21] [22]. Medical doctors established the prognosis using the News 2 score and evaluated the need for transfer to hospitalization (News > 4) or intensive care. Patients with abnormal ECGs or QTc > 460 ms and/or K< 3.6 mmol/l and/or receiving drugs not compatible with HCQ were contraindicated for HCQ and treated with AZT/Zinc. The remaining patients were asked if they wished to be treated with the combination of HCQ/AZT/Zinc. Outpatients with a comorbidity or older than 55 were advised to monitor their oxygen saturation at home, even if they felt comfortable, and to consult their doctor immediately if the Sa02< 95% on two occasions [23]. In patients with a risk of thrombosis we prescribed anticoagulant therapy. When the D dimers were above 0.5 µg/ml a doctor called the patient back and prescribed anticoagulant therapy, and if > 2 µg/ml the patient was asked to present immediately for a CT angiogram to rule out pulmonary embolism. All patients were systematically told to come back to the hospital in case of need. All patients were asked to come back at day 10 for PCR testing [24].

The same protocol was applied to patients treated in the IHU wards. All patients were offered HCQ/AZT/Zinc if they volunteered and had no contraindications [25, 26]. The treatment protocol was adapted during the progression of the outbreak with the addition of anticoagulant therapy, steroids (dexamethasone 6 mg/d) for severely ill patients requiring oxygen and in the inflammatory phase of the disease when the CT indicated that the viral load was either negative or very low, and finally with high flow oxygen therapy in patients for whom the intensive care unit was not indicated [Lagier J.-C. et al., in this CID issue]. To accelerate patient rotation and enhance the capacity of the IHU to isolate contagious COVID-19 patients, we transferred all patients exhibiting 2 negative SARS-CoV-2 PCR, defined as a CT>34 based upon our own laboratory data, to other units [27]. Every morning a general staff meeting was held to adjust patient care (see above).

Results.

From March 5, 2020 to January 5, 2021 (10 months) at the IHU, we conducted 401,390 SARS-CoV-2 PCR tests for patients in our institution (AP-HM, including IHU) and for people coming from everywhere in the French territory. Of the 203,381 patients tested at our institution, 20,173 (10%) were positive for SARSCOV 2; of them, 15,635 were from the IHU screening facility. Of these, we treated 11,339 COVID-19 patients in the day hospital and 1,888 in infectious disease wards. We conducted 5,250 low-dose CT scans of the lung and 14,857 ECGs (Table 1). The COVID-19 epidemic provided the opportunity to rapidly assess the performance of new diagnostic assays and tests, given

the large amount of well-preserved, well characterized, anonymized clinical samples in the biobank, as for antigen testing [28].

This intense activity in COVID-19 diagnosis and research in the IHU yielded a total of 21 preprint articles posted on three different platforms, including the IHU web site for preprints, and 155 published and accepted for publication as papers in 84 different journals. The current total citations are 3,824 (Web of Science). Also, a total of 132 videos, consisting of information videos and tutorials for patients and physicians posted on the IHU Youtube channel, totaled almost 46 million views, with 330,000 followers (January 18th, 2021).

Conclusion. The successful diagnosis of COVID-19 and treatment in the IHU relied upon: (1) leadership, (2) autonomy in decision-making with immediate, supervised enforcing of decisions, (3) previous expertise in pathogen diagnosis, (4) detournement of instruments, (5) rerouting of tests: re-using ELISA plates three times after they were appropriately washed without significant loss of technical performance, after laboratory validation. Technical autonomy will be increased by an on-going facility developing PCR primers and probes production (OligoMaker 48; OligoMaker ApS, Copenhagen, Denmark). Unrestricted access to care, collection of patient medical records and regular analysis of signs and symptoms [Brouqui P. et al., in this CID issue], analysis of risk factors and patient outcomes, permanent adaptation of treatment protocols, well-organized monitoring of outpatients, early care and treatment based on the most efficient and/or the least toxic available drug, and proximity of the laboratory are the main pathways for success.

Acknowledgments

This manuscript has been edited by a native English speaker.

Figure legend:

Figure 1: IHU organization pathway for testing and microbiology analysis, care, and research on outbreaks using the example of COVID-19, March 2020 – January 2021. Research is at the interface of the laboratory, divided into a Point of Care (POC) and Core laboratory; treatment, divided between the outpatient clinic and 75 bed wards, and BSL3 activities. Patient entry left and exit right.

Table 1: Results of COVID-19 diagnostic care and research at IHU MI on January 5th, 2021.

Supplementary data. Functional organigram of the Foundation Méditerranée Infection, the legal structure supporting IHU Méditerranée Infection, Marseille, France. conveniently located in the heart of the medical university hospital campus, Marseille, France.

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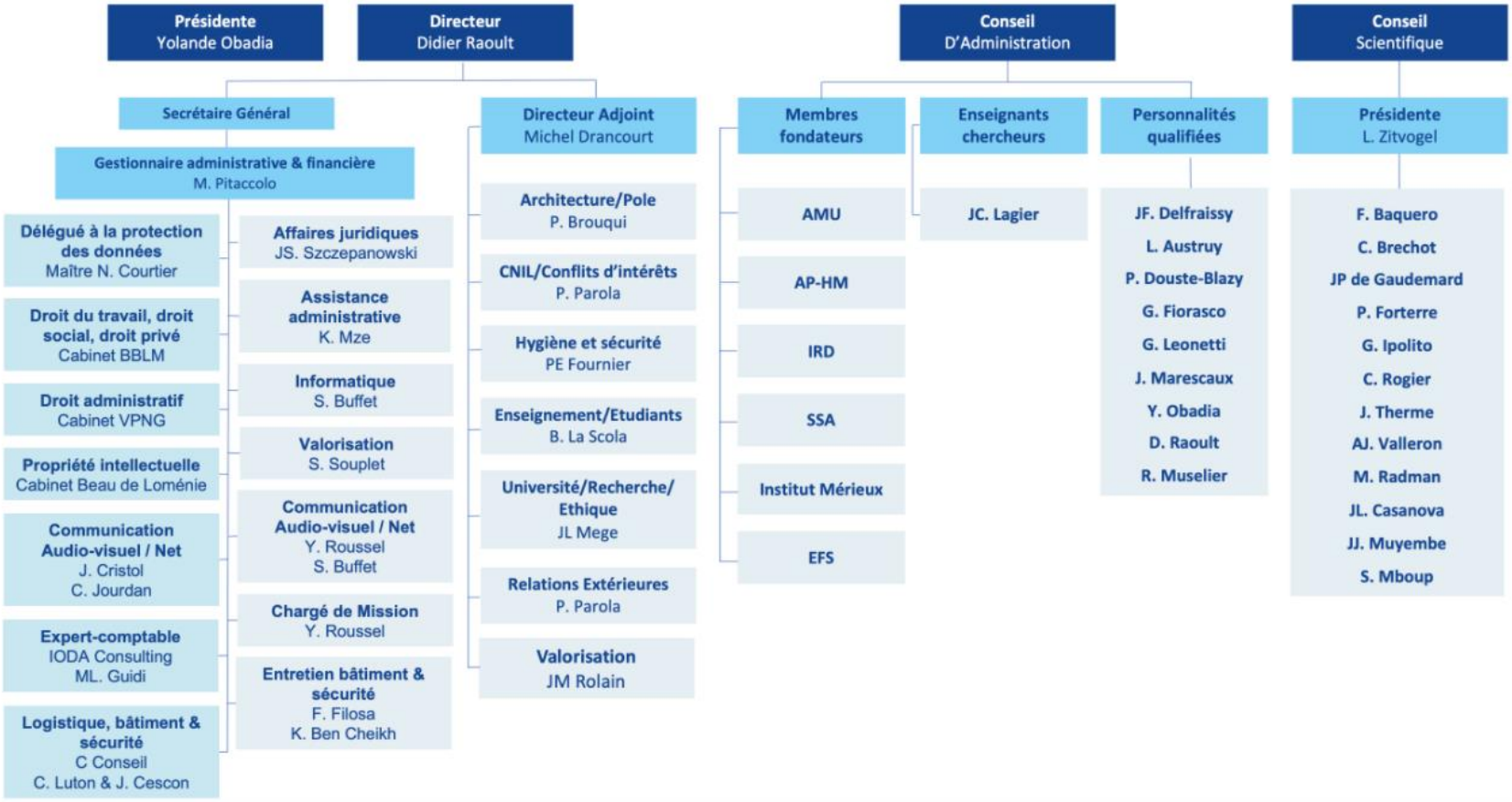

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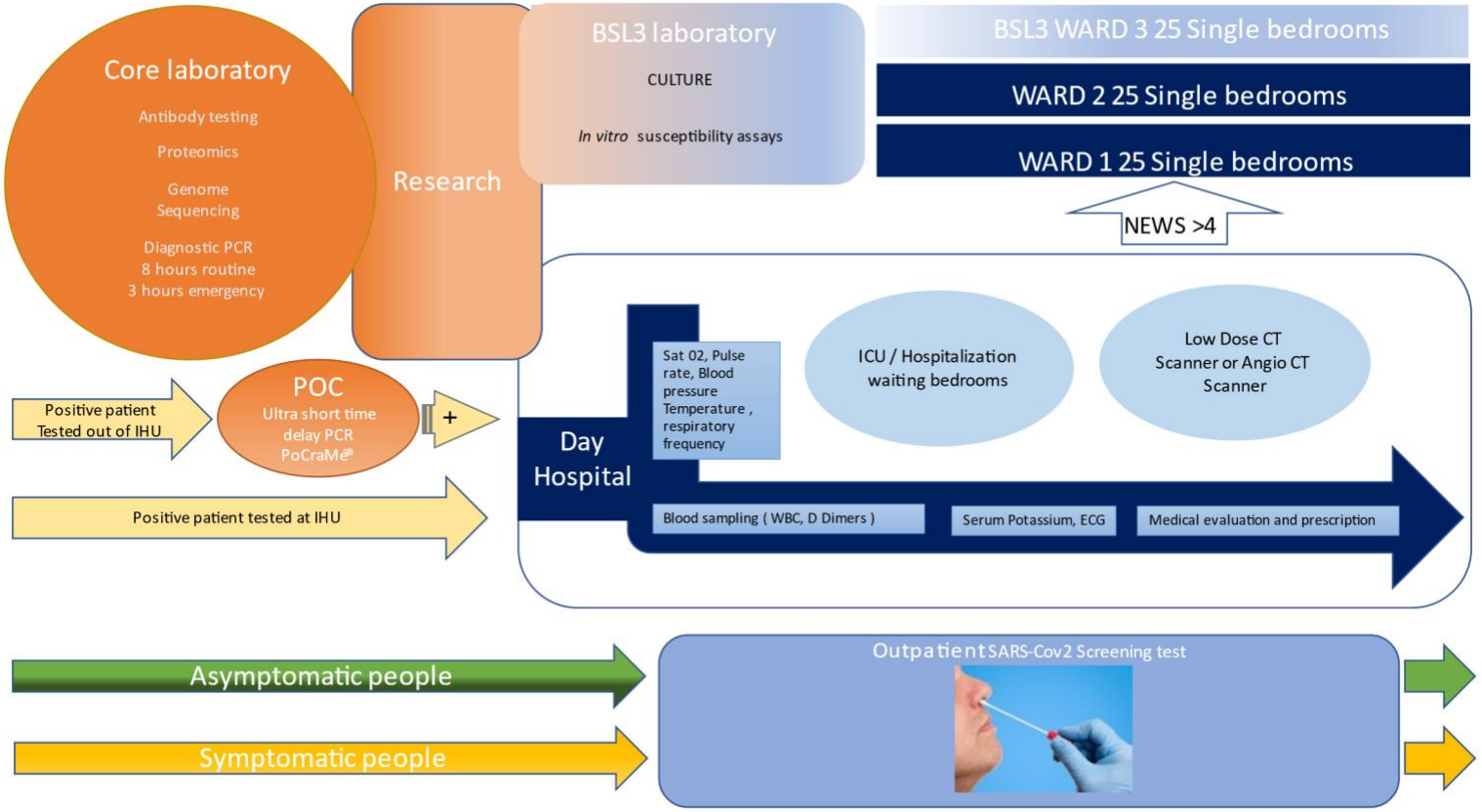
Core laboratory
Antibody testing
Proteomics
Genome Sequencing
Diagnostic PCR
8 hours routine
3 hours emergency
Research
BSL3 laboratory
CULTURE
In vitro susceptibility assays
BSL3 WARD 3 25 Single bedrooms
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WARD 1 25 Single bedrooms
NEWS >4
Positive patient Tested out of IHU
POC
Ultra short time delay PCR
PoCraMé®
+
Positive patient tested at IHU
Day Hospital
Sat 02, Pulse rate, Blood pressure Temperature , respiratory frequency
ICU / Hospitalization waiting bedrooms
Low Dose CT Scanner or Angio CT Scanner
Blood sampling (WBC, D Dimers)
Serum Potassium, ECG
Medical evaluation and prescription
Asymptomatic people
Symptomatic people
Outpatient SARS-Cov2 Screening test

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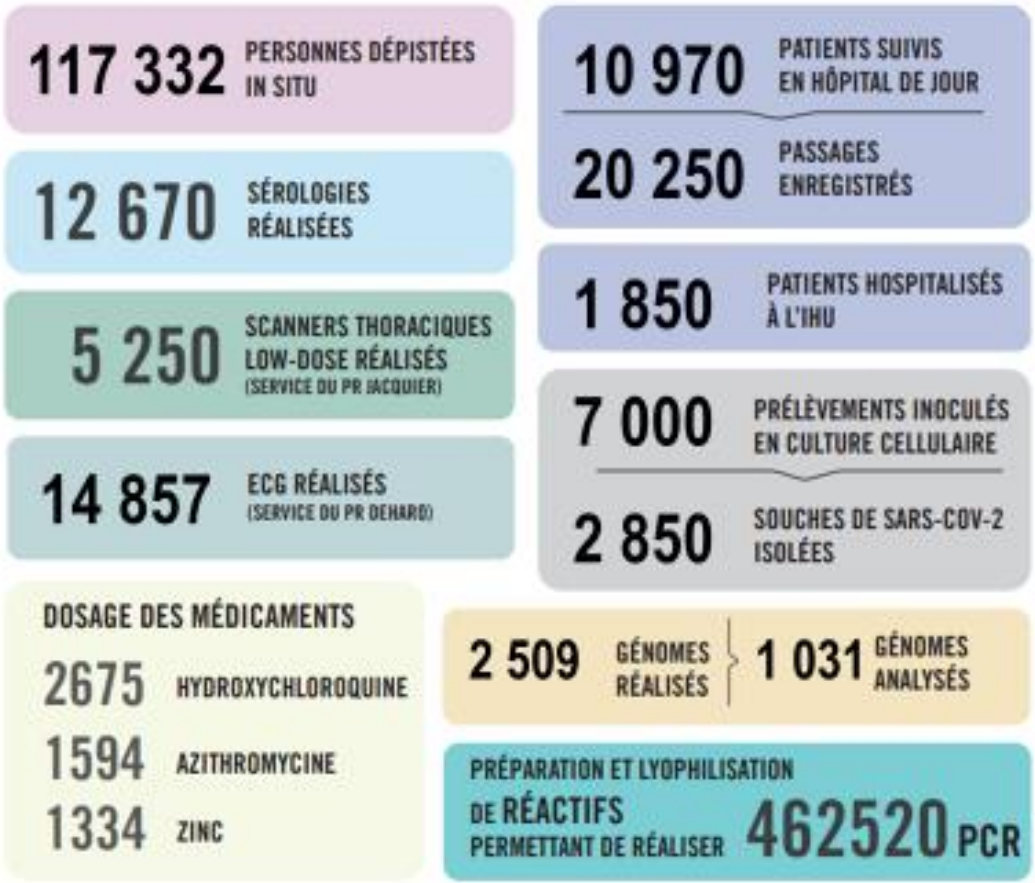
Table 1 : The COVID-19 pandemic: 10 months key data at IHU MI



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