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Preparedness of European diagnostic microbiology labs for detection of SARS-CoV-2, March 2020



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ABSTRACT

Background: To track the European spread of SARS-CoV-2, decentralized testing became necessary and test capacity needed to be expanded outside reference laboratories rapidly.

Methods: We assessed via an online questionnaire the preparedness of European hospital laboratories for detection of SARS-CoV-2 and listed the main drawbacks for implementation.

Results: Forty-five percent of the surveyed labs had a test in place by March 26th which is well into the first wave of the pandemic in most countries.

Conclusions: The main implementation barriers for introduction of a SARSCoV-2 molecular assay in European diagnostic laboratories were availability of positive controls and a specificity panel.

1. Introduction

SARS-CoV-2 associated pneumonia cases were first described in Wuhan, China in December 2019. Despite massive efforts in China and elsewhere to contain the spread, the virus has been dispersed globally and COVID-19 was declared a pandemic by the director of the WHO on March 11th [1]. The SARS-CoV-2 viral genome sequence was released on January 10th via the community online resource virological.org [2] followed by formal publication by the Chinese government on January 12th, which was of great importance to start the development of specific diagnostic tests for the detection of this emerging respiratory pathogen [3]. The rapid deployment of diagnostics was decided in view of lessons learned on the potential for global spread and seeding of outbreaks internationally from SARS-CoV-1 and MERS. The initial WHO strategy for containment of SARS-CoV-2 was rapid identification and follow-up of cases linked to affected countries in order to minimize onward transmission. This approach rapidly shifted to a broader screening approach as local transmission within European countries occurred, with the need for increased test capacity, exceeding that of the national reference laboratories that had been implementing diagnostics as part of their preparedness activities [4]. WHO responded with a dedicated webpage listing certain specific laboratory tests for

molecular detection of SARS-CoV-2 to be implemented [5]. Also ECDC provided online laboratory guidance by recommending laboratories to have their first 5 positive cases and 10 negative ones confirmed by a (inter)national reference lab for SARS-CoV-2 and to test independently thereafter but in collaboration with reference labs to troubleshoot any assay issues [6].

2. Methods

Our laboratory questionnaire was organized as part of the EU funded research project named “Rapid European COVID-19 Emergency Research response (RECOVER)”. The survey was sent out on January 29th to 306 laboratories already participating in the established research networks of COMBACTE LAB-Net (Combatting bacterial resistance in Europe, www.combacte.com) and PREPARE (Platform for European Preparedness Against (Re-)emerging Epidemics, www.prepare-europe.eu). Active aggravation of participants was organized through sending out reminder emails which resulted in a response rate of 28% (87/306) on March 26th. The main purpose of the survey was to assess the preparedness of laboratories to implement a molecular test for detection of SARS-CoV-2 and to pinpoint the main challenges of the labs in order to develop a specific laboratory supportive strategy as part

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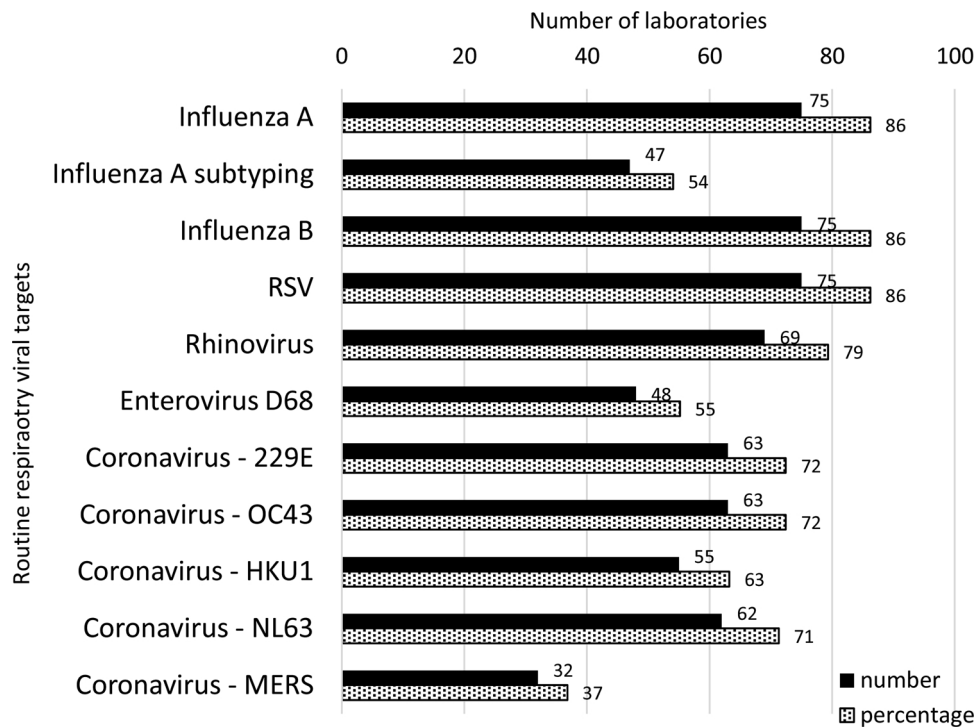


Fig. 1. routine molecular testing for respiratory viruses in participating laboratories (n = 87).

of the RECOVER project.

3. Results

3.1. Laboratory characteristics

Eighty-seven diagnostic laboratories from 23 different European countries replied to the survey: Belgium (12), the Netherlands (10), France (9), Spain (7), Romania (7), United Kingdom (6), Germany (4), Switzerland (4), Bosnia and Herzegovina (3), Serbia (3), Albania (2), Austria (2), Bulgaria (2), Czech Republic (2), Estonia (2), Hungary (2), Italy (2), Kosovo (2), Sweden (2), Finland (1), Lithuania (1), Norway (1) and Turkey (1). Most labs already perform routine molecular diagnostic testing for respiratory viruses, predominantly for influenza A, B and RSV (Fig. 1). Most laboratories (n = 64) have a Biosafety Level (BSL) 2 license, which is required for non-propagative diagnostic work on SARS-CoV-2 (e.g. nucleic acid amplification) and about half of them (n = 44) also has a BSL-3 facility which is necessary for SARS-CoV-2 viral culture [5]; 56 labs perform molecular testing in a laboratory with ISO 15,189 accreditation for medical laboratories. 64% of the labs already has experience in rapid implementation of molecular tests in a timeframe of 1 week (46%), 2 weeks (34%), 1 month (18%) or later (2%).

3.2. SARS-CoV-2 molecular test specifics

Considering implementation of a molecular test to detect SARS-CoV-2, 45% of the labs already implemented a test, 38% of the labs considers implementation and the remaining 17% will not introduce such a test in their lab (Fig. 2). Of those who implemented or will implement SARS-CoV-2 molecular testing (n = 72), 87% of 32 labs answering this specific question, will achieve or achieved this goal within a month's time (Fig. 2). The specific gene targets in case of an in-house molecular test (n = 50) are mostly the envelope (E) gene (82%) and RNA-dependent RNA polymerase (RdRP) gene (64%), followed by the nucleocapsid (N) gene (38%). The most commonly used commercial tests (n = 17) were Novel Coronavirus Strain 2019-nCoV (Genesis by Primer Design)

(n = 5), Cobas SARS-CoV-2 test (Roche) (n = 3) and RealStar SARS-CoV-2 RT-PCR kit RUO (Altona diagnostics) (n = 2). Five labs had not decided yet on the type of assay to introduce. Seventy-nine percent (n = 57/72) of the labs will validate their test at least partly against other coronaviruses and most common respiratory pathogens. Positive control material will be used by 94% (n = 68/72) of the labs and an internal process control by 85% (n = 61/72). Sample types that will be used for SARS-CoV-2 detection are a wide range of respiratory samples, predominantly the non-invasive sampling of nose and throat (Fig. 3). Five labs suggested using additional sample types like saliva, feces, urine, CSF and blood. Indeed, SARS-CoV-2 has been detected in secretions other than respiratory [7,8]. The daily test capacity varies among the labs with 41% being able to process over 50 samples a day. Seventy-nine percent of the labs would generate a result within 24 h. Participation in an external quality control program for SARS-CoV-2 detection, when available, is an objective of 82% of the labs (Fig. 3).

3.3. Implementation challenges and drawbacks

Of the 72 labs having a SARS-CoV-2 test in place or willing to implement one, 31 (43%) indicated that they require support. This support is explicit for the provision of positive controls (97%) and a specificity panel (81%) for validation purposes. Other needs are confirmatory testing at a central laboratory (52%), provision of an analytical SOP (32%), sampling SOP (26%) and shipment SOP (23%). For all the 87 labs answering the questionnaire, the top 5 main challenges for implementation of a SARS-CoV-2 molecular test are lack of personnel/time (53%), lack of funding (45%), lack of positive control (38%), lack of equipment (31%) and lack of a commercial test (29%) (Fig. 4).

4. Discussion

SARS-CoV-2 positive cases are rapidly increasing globally. As of April 1st 2020, 464,857 cases including 30,098 deaths were reported among 53 countries in the WHO European region [9]. Timely detection of SARS-CoV-2 remains crucial to control further spread of the virus and

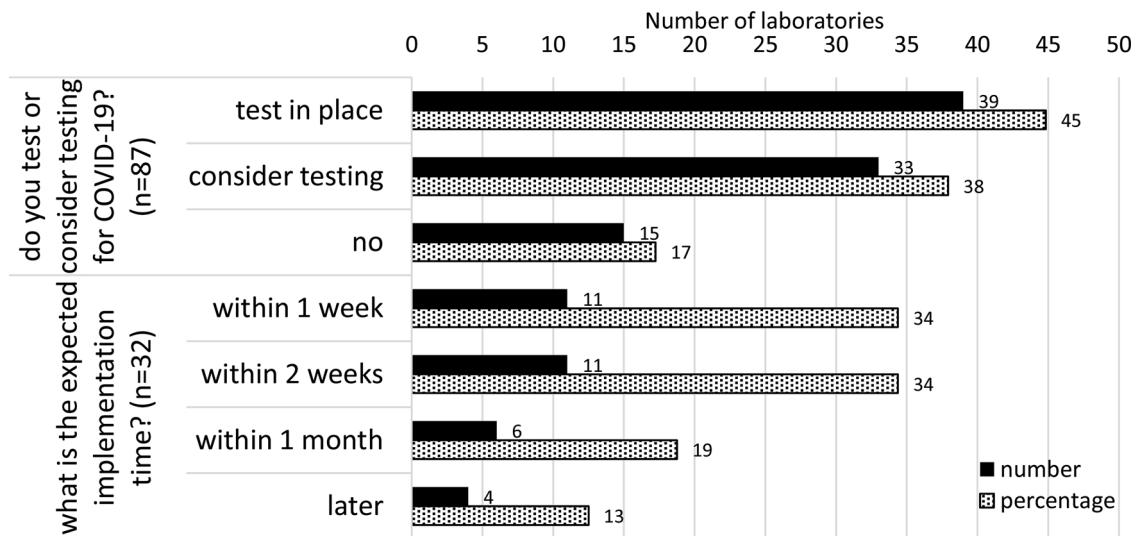


Fig. 2. Plans and realizations considering SARS-CoV-2 molecular testing and timeframe for implementation in participating laboratories.

as the SARS-CoV-2 outbreak turned into a pandemic, test capacity needed to be extended to routine diagnostic laboratories, instead of reference laboratories only. We send out this questionnaire in the same time frame as a survey among reference laboratories, which had a turnaround time of less than a week. Here, with repeated requests, the response rate was 28% over a 5 week period. This observation suggests that the level of preparedness for this type of activity in hospital

laboratories may not be sufficient. The main challenges that the labs face are comparable to those of reference laboratories [4], except the need for commercial tests that is, according to expectation, not expressed by reference labs. Remarkable are the requests for support in provision of positive control material and specificity panels as those have been made available at the European Virus Archive (EVAg) soon after publication of protocols on the dedicated WHO website [5]. These

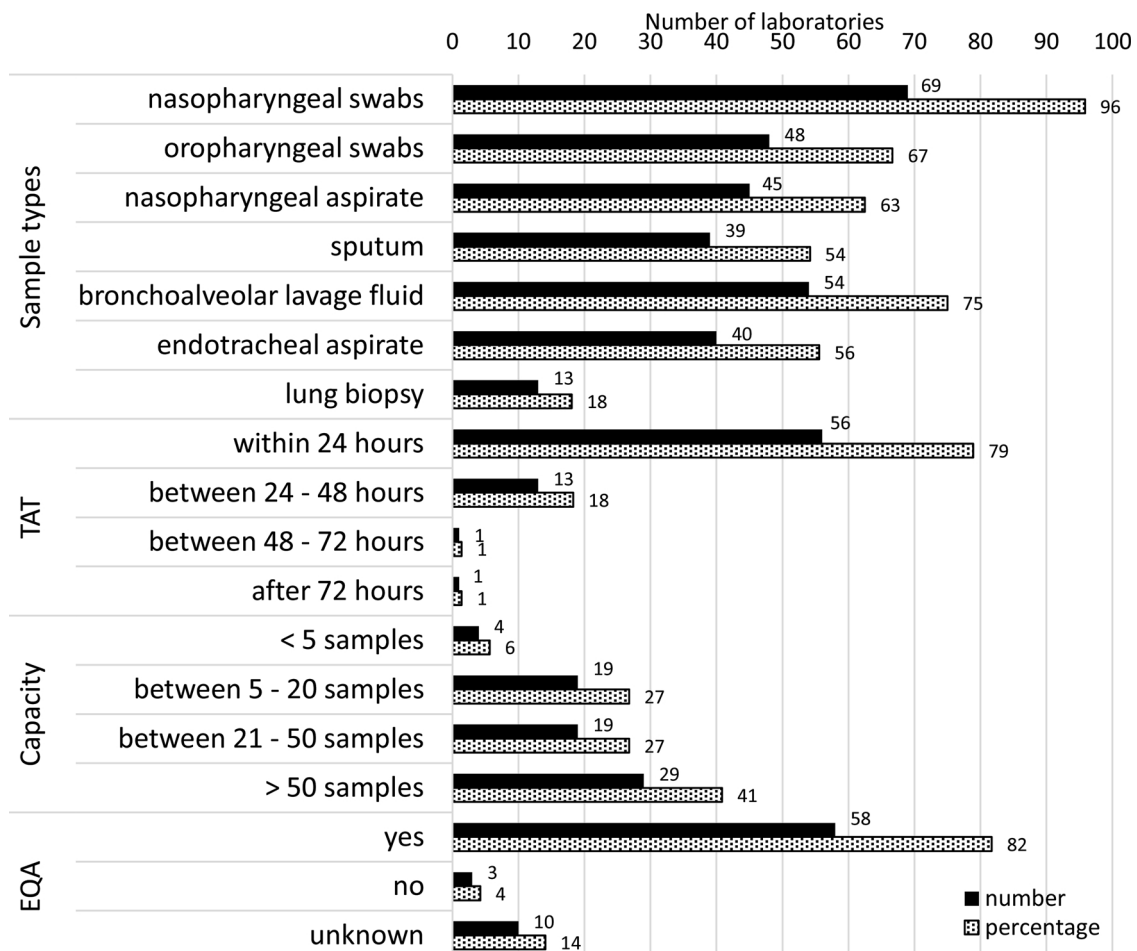


Fig. 3. Sample types, turn-around-time (TAT), daily capacity and external quality control or SARS-CoV-2 molecular testing in participating laboratories (n = 72).

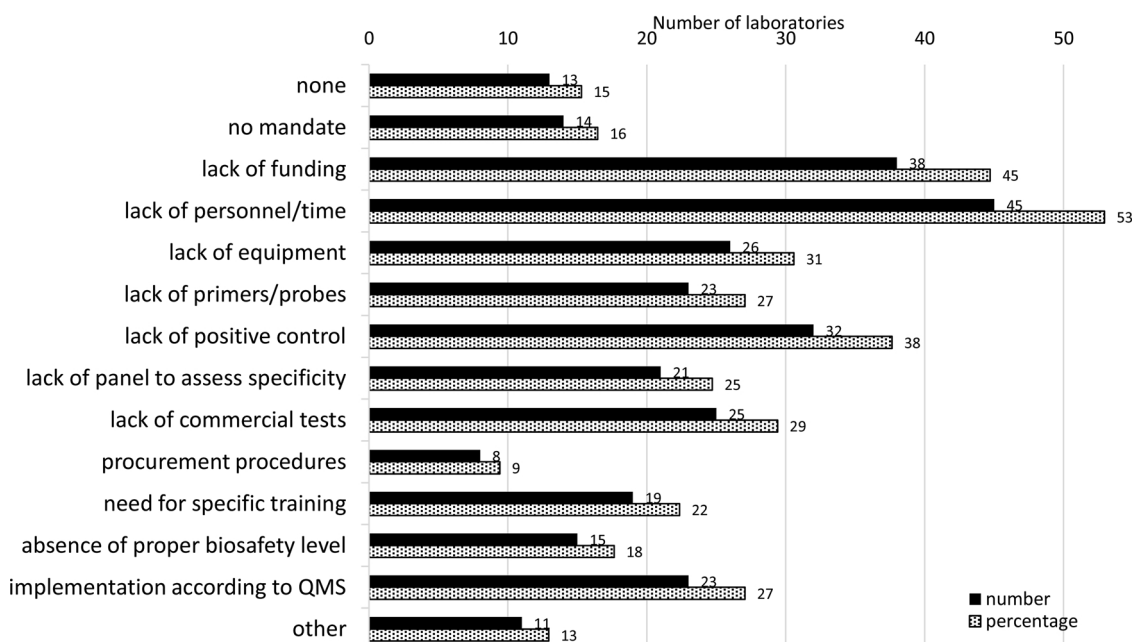


Fig. 4. Main challenges for implementation of a SARS-CoV-2 molecular test in participating laboratories (n = 85).

materials, positive control and specificity panel, are of course crucial for validation of clinical sensitivity and specificity respectively. This finding implies that diagnostic labs might not be aware of the existence of these organizations. Reference laboratories could play a crucial role in providing this informative support to diagnostic labs. At the time of publication, access to positive samples will however not be problematic anymore as laboratories will have had access to positive patient samples by now due to the drastically increased number of infected people. Another crucial part of assay validation is proficiency testing. The vast majority of labs are willing to participate in SARS-CoV-2 specific EQA programs, which are being put in place by EQA organizations like Quality Control for Molecular Diagnostics (QCMD) at this moment.

Around 30% of the surveyed labs is awaiting the launch of commercial assays as they are not experienced with molecular assay development. However, this is a well-known misunderstanding: the availability of validated commercial assays requires several months after emergence of an infection, a point that has been difficult to address in between health emergencies [10]. This was further compromised by the shut-down of the global market as part of the control measures in this epidemic, which had major impact on available resources, showing the dependence of clinical sites on major platforms. Currently, multiple commercial assays are on the market and even point-of-care platforms have recently received FDA approval e.g. Xpert Xpress SARS-CoV-2 (Cepheid) on March 21st, BIOFIRE COVID-19 (bioMérieux) on March 24th and ID NOW COVID-19 (Abbott) on March 27th. As a result, COVID testing will be accessible for those labs not equipped for non- or semi-automated real-time PCR and/or do not have the required expertise for in-house assay development, assuming shortages will not apply, which is unlikely. FDA approved tests only need verification instead of more intensive validation before implementation and therefore can be introduced in routine practice more rapidly [11].

5. Conclusions

In summary, many European diagnostic laboratories have made efforts to implement a molecular test for SARS-CoV-2 detection and many are planning to do so. Challenges mentioned are access to and availability of control material for assay validation, although this clearly indicates a lack of awareness of national and international

preparedness programs and resources, as controls and reference panels have been provided as early as January through EVAg. Test capacity expansion will be the main challenge as this pandemic progresses, and proper validation of the different assays is key.

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CRediT authorship contribution statement

Veerle Matheussen: Conceptualization, Writing - original draft, Visualization. **Katherine Loens:** Conceptualization, Writing - review & editing. **Christine Lammens:** Conceptualization, Software, Project administration. **Tuba Vilken:** Conceptualization, Software, Project administration. **Marion Koopmans:** Conceptualization, Writing - review & editing. **Herman Goossens:** Conceptualization, Funding acquisition. **Margareta Ieven:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

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