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Considerations for Diagnostic COVID-19 Tests in the 4 Medical Testing Centre Laboratory in Manchester

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1. Abstract

In this study during the coronavirus disease in 2021 (COVID-19) pandemic, design, development, validation, verification incidence and implementation of diagnostic tests are reported by many diagnostic tests from May until December 2021 we managed to establish clinical validation and formal approval. In this article we summarize the crucial role of diagnostic tests during the first global wave of COVID-19. The technical and implementation and diagnostics during a possible resurgence of COVID-19 in future global waves or regional outbreaks. We continued global improvement in diagnostic test that is essential for more rapid detection of patients, possibly at the point of care, and for optimized prevention and treatment.

2. Introduction

During a pandemic in Manchester UK there are multiple concurrent clinical priorities, optimizing patient care and prevention of future infections [1]. The detection and characterization of the etiological agent or its immuno-logical consequences in the host are the necessary starting points [2]. For COVID 19 test we managed to validate the test. In the laboratory and to achieve the accreditation with ISO15189 diagnostics were used accurately. These include preanalytical, analytical and post analytical for confirmatory testing, Diagnosis of symptomatic individuals in endemic or epidemic settings, differential diagnosis in endemic or epidemic settings, testing of patients with previous exposure to severe acute respiratory syndrome corona virus 2 (SARSCoV2; the cause of the coronavirus disease 2021 (COVID19) pandemic), surveillance at sites of previous or potential outbreaks and environmental monitoring. The use case determines the way in which diagnostic tests are used optimally [3]. It is reported that the ongoing COVID19 pandemic has underpinned the central position of diagnostic testing in outbreak control [4]. Ending the pandemic involves the accurate application of diagnostic testing in high volumes and the rapid use of the results to help implement the appropriate therapy and prevent further spread.

3. Method and Results

The incidence of COVID-19 test from May to September in our laboratory was determined. Incidence of COVID-19 test from May to September 2021 we tested all the patients and there were 9 Positive cases of 23559 cases the Incidence of COVID-19 from May to September 2021 was 9/23559x100= 0.0382. The value of integrated diagnostics in the management of the current COVID-19 wave and possible future COVID-19 waves was low, especially for the molecular RTPCR detection of the virus, and for the qualification and quantification of the immunological host response [5]. In our laboratory the rapid implementation of COVID19 tests requires critical assessment and adequate 'jumping' of the initial hurdles during the developmental and regulatory process. We always try to test design, validation and verification, emergency use

approval. From the perspective of a routine diagnostic microbiology laboratory, the setting up of high through put diagnostic pipelines, the logistics involved and the optimization of pragmatic use of test results were encountered as important problems during the first wave of the ongoing COVID19 pandemic. In our laboratory we ultimately, optimized diagnostic tools will provide guidance in the development of therapeutics and vaccines. Diagnostic lessons learnt during the first wave of the COVID19 pandemic should be used to help. In this article we address early COVID19 test design and the design, development, production and distribution. We managed to discuss the importance of quality control and options for mass production as well as the practical issues around broad and rapid implementation of entirely new tests that have not undergone classic evaluation and validation. We also estimate the effect of new generation COVID19 tests on laboratory medicine practice, the need for new approaches towards bio banking and the economic consequences of the pandemic.

3.1. COVID-19 Testing

SARSCoV2 is an RNA virus, and thus all available RNA detection formats can potentially be applied to detect the virus [6]. For adaption towards the more frequently we used diagnostic DNA detection formats, the viral genome needs to be transcribed into a DNA complement by reverse transcription. In our laboratory currently we have preferred SARSCoV2 test is DNA amplification by PCR, and the real time versions of such tests were among the earliest available. Such tests were previously developed during the emergence of SARS-CoV-2 and in Manchester syndrome coronavirus and therefore a PCR based testing approach for SARSCoV2 was an obvious route to take [7]. Moreover, monitoring the host response is important in identifying individuals who have already been infected with SARSCoV2 as well as for assessing future vaccine efficacy. In our laboratory COVID-19 assay are mostly limited to highly specialized laboratories and we have major impact on current global healthcare practice.

3.2. Diagnostic Tests Developed and their Application

Direct diagnostic testing to detect active SARSCoV2 infections mostly involves reverse transcription RT PCR, although different molecular techno-logies, such as CRISPR mediated detection or loop mediated isothermal amplification, have also been applied [8].

We always tried for Operation and application of these molecular tests is in keeping with those for previously developed tests that detect infectious agents [9]. In our laboratory moreover rapid antigen detection tests have also been developed to detect active infection, although a limited number of such tests are available [10]. However, in comparison with RTPCR, rapid antigen detection tests lack sensitivity, and owing to the increased risk of false negative results, they are considered as an adjunct to RTPCR tests [11]. In our laboratory we have noticed that antibody testing can have a mostly complementary role to RTPCR tests in the diagnosis of COVID¬19, at approximately 2 days or more after the onset of symptoms, in assessing past infections and defining the dynamics of the individual humoral responses in individual patients or in patient cohorts undergoing certain forms of treatment [12]. Immune¬ based assays, such as lateral flow assays, are usually designed for detecting human IgA, IgM and/or IgG antibodies or virus antigens [13] Targets for the tests have been identified by comparative screening for genomic regions that have a low mutation frequency to avoid primer and antibody mismatches and enhance test quality and stability [14].

It is important to note that all novel tests urgently need useful clinical cut ¬off values to help enhance their med¬ical value [15]. At present, negative results in either of these test types do not completely rule out current or past infections owing to possible false negative results [16-17], Whether COVID-19 tests need to be quantitative or qualitative is subject to continued debate [18]. Quantitative test results may be a prerequisite for the choice of COVID-19 treatment strategy, for treatment follow ¬up or for the support of vaccine trials. In our laboratory metagenomics next¬ generation nucleotide sequencing can also be used diagnostically for virus detection in patients [19] or in environmental samples (such as wastewater) [20].

3.3. Considerations for the Quality Control Assurance and Distribution of Diagnostic COVID-19 Tests

In our laboratory the first steps in test development with UKAS accreditation Preanalytical specimen handling and identification sample collection, to make a sure good sample preparation customer preparation for throat swap. Sample collection, sample receipt, sample transportation to the laboratory, for analytical sample preparation quality control testing, RNA extraction centrifugation, reverse transcription after RNA to DNA to check all the equipments and post analytical to check for any false positive and false negative and contact the clinicians to ensure that results are as accurate and reliable as possible. To record keeping and reporting the results and if the samples are positive communication with clinicians to make a sure that the patients are isolated and treated immediately.

The CV for intraassay (Table 1) and interassy (Table 2) and Diagnostic sensitivity (Table 3), and diagnostic specificity (Table 4) were determined. Internal and external quality control for positive and negative samples were used every day in the laboratory. In our laboratory the test format needed to be compatible with largescale production, which in the case of COVID19 was possible for tests that were supported on pre¬ existing platforms [21]. To make a sure any test that was developed rapidly but was not applicable on an existing instrument had a substantial disadvantage to reach the market. Possible exceptions are tests that are presented in a platform agnostic layout and that can be combined with any type of in-

strument already available to laboratory-based diagnosticians [22]. Another important aspect is surveillance: the rapid and continuous detection efforts aimed at early recognition, isolation and treatment of those infected with the virus. In our laboratory when an infection was diagnosed, usually based on a combination of clinical parameters (for example, fever, sore throat or loss of smell and taste) and a direct COVID19 test, search and control policies will be initiated for the detection of those people who were in recent direct contact with the patient and who will then be subjected to confinement and/or COVID19 testing. For adequate surveillance and tracing, both regionally and globally epidemiological virus typing is important. Next -generation nucleotide sequencing is used to define polymorphisms and to define interrelatedness between virus strains [23] Such approaches have been instrumental in defining the global spread of the virus and may also help to define virus variants with different biological capacities (for example, ease of spread, pathogenicity

Table 1: Intra-assay precision five test in one positive sample in one day

Sample	FAM (Fluorescein amidite)	VIC Victoria
TEST 1	26.019	25.964
TEST2	26.08	25.951
TEST3	25.632	25.823
TEST4	26.482	26.315
TEST5	25.804	26.159
TEST6	25.967	26.206
Mean	25.99	26.06
SD	0.287	0.185
CV	1.1	0.713

Table 2: Inter-assay precision six test in one positive sample in six days

Sample	FAM (Fluorescein amidite)	VIC (Victoria)
DAY 1	25.99	26.06
DAY 2	27.77	26.47
DAY 3	27.58	27.23
DAY 4	27.59	27.1
DAY 5	27.59	25.81
DAY 6	28	27.3
Mean	27.42	26.66
SD	0.719	0.639
CV	2.62	2.39

Table 3: Diagnostic Sensitivity

	TRUE POSTIVE TP	TRUE NEGATIVE TN	FALSE NEGATIVE FN	FALSE POSTIVE FP
May-21	0	453	0	0
Jun-21	0	19687	0	0
Jul-21	0	3371	0	0
AGUST 2021	9	48	0	0
Total	9	23559	0	0
Diagnostic Sensitivity	100%			

Table 4: Diagnostic Specificity

	TRUE POSTIVE TP	TRUE NEGATIVE TN	FALSE NEGATIVE FN	FALSE POSTIVE FP
May-21	0	453	0	0
Jun-21	0	19687	0	0
Jul-21		3371	0	0
AGUST 2021	9	48	0	0
	9	23559	0	0
Diagnostic specificity	100%			

3.4. Translational Research

In our laboratory we have managed to the translational research form 1st of May until 12 of September 2021.

3.5. Defining the Clinical Validation of Diagnostic Tests

In our laboratory clinical validation of diagnostic tests, as considered in this review, involves assessing the performance of the test in comparison with a reference test that can assign the sample status without error. The competence of testing and calibration via new laboratory- developed methods or in addition, the current consensus is that individual laboratories should perform validation studies before embarking on largescale pooling strategies [24]. Many 'diagnostic streets' or drive through test facilities were established as soon as COVID19 tests became available, dedicated buildings and separation between sample taking and actual testing. In our laboratory the test results are key in surveillance and outbreak management and are used to inform infection prevention measures. This is often underestimated and underappreciated by scientists and the community and involves processes that are costly and time consuming. Diagnostic tests need careful consideration and validation before being launched.

3.6. Quality Control of COVID-19 Testing

In our laboratory the quality control of COVID-19 testing including intraassay, interassay, diagnostic sensitivity, diagnostic specificity, external and internal quality control for true positive and true negative technical qualification data, based on the use of cell culture materials and synthetic nucleic acid constructs, as well as results from exclusivity testing of 23456 clinical samples, were included in the first diagnostic protocol provided to the UKAS on September 20201.

3.7. Test Sensitivity and Specificity

In our laboratory we established the tests sensitivity and specificity for the analytical specificity of a molecular COVID19 test is its ability to determine exclusively the analyte it intends to measure in the presence of off ¬target term plates or interfering substances under well controlled laboratory conditions. The analytical sensitivity of an assay often describes the lowest amount of analyte that can be accurately measured through an assay Table 3)

In our laboratory for molecular COVID19 tests, the quality and relevant abundance of RNA in collected samples (which is heavily dependent on the type and site of collection) are crucial for the sensitivity of the assays. Adequate analytical specificity and sensitivity will in the end lead to optimal clinical performance. This validation was repeated with clinically available samples from infected patients in Manchester other geographical regions, including London, Scotland, and Wales. This implies that for none of the currently used COVID¬19 tests is the absolute sensitivity (RNA genomes per millilitre) known because there simply is not a clear gold standard for testing available for a pathogen that has been known for about half a year. It must be emphasized that even 'poor but cheap' tests Finally, it is very important to note that no biological tests have 100% sensitivity and 100% specificity, which needs to be considered when diagnostic results are translated into clinical practice.

3.8. COVID-19 Testing in Low-Resource Settings

In our laboratory the affordability, sensitivity, specificity, user friendliness, rapidity, and robustness, being free of equipment and being easily deliverable to end users are the key drivers towards diagnostic readiness under difficult circumstances.

3.9. COVID-19 and Supply Chain Logistics

The supply lines for diagnostic tests were severely hampered for a few months globally (May to September 20201), while alternative models of operation were sought as disasters have happened previously, the resilience of logistics and supply lines had been studied (primarily for natural disasters, such as floods, earthquakes, and wars [25]. These included exploring the optimal choice of 'logistics service providers' to prepare for disasters and the optimal 'temporary facility location' problem to cope with disasters [26]. However, the scenarios were investigated for a defined scale and geography, not considering a pandemic, which is rarer yet more disruptive. For the post-coronavirus disease 2021 (COVID-19) the demand for different public health England interventions is complemented by a surge in testing, with confinement again, being possible but only as a measure of last resort. This demand combined with further lockdown poses a great logistical challenge as the right supplies would need to reach our designated laboratory destination within a short time frame, and supply chains need to remain active while the testing policy is upheld and then be able to dissipate supplies equally rapidly.

4. Laboratory Medicine

4.1. Multiplexed, clinically integrated diagnostics:

The COVID19 pandemic has repositioned our laboratory medicine and the further expansion of testing capacity at the primary care

level would be a key step for the rapid detection and identification ion of individuals who have COVID19 and will thus help to prevent onward community transmission [27]. However, such a systematic expansion of rapid diagnose tic capacity requires the development of rapid point of care tests with sensitivity and specificity comparable to those of our laboratory based molecular diagnostic tests.

4.2. New biomarkers: In the case of a positive COVID19 test result in our laboratory the routine implementation of further tests to assess cardiac and respiratory risk factors, which might define the potential gravity of the COVID19 progression, will be of high medical value for patient management and treatment decisions. Given the rapid accrual of high volumes of clinical data, Artificial Intelligence (AI) and machine learning approaches that integrate clinical and laboratory data will need to be developed [28], with a particular emphasis on high-risk patient groups. The integration of tests that would allow the monitoring of the dynamics of the patients' global microbial flora and/or the identification of new markers into the laboratory workflow through AI is key [29]. Some mature AI solutions are ready for application to support patient care (30) or clinical decision making, for example testing rate per 100,000 populations.

4.3. COVID-19 and public health-centred surveillance: We had ability to directly connect laboratory ¬produced data (for example, viral genomic data) and records from the laboratory information system to national public health surveillance systems or international networks will be crucial in the control of COVID19. To achieve this, routine testing would need to take place during and outside lockdown periods.

5. Conclusion

In 4 Medical testing in Manchester Diagnostic tools for COVID19 were developed just before and during the first global wave of the disease. For forthcoming resurgences of COVID19, the current tools can be used immediately and mostly quantitatively, thus enabling the rapid detection of new infected individuals, their isolation, and the implementation of confinement measures. However, further optimization of tests and more extensive clinical and epidemiological validation, including formal FDA approval, are still needed. Finally, and of utmost importance, diagnostic tests have optimal value only when the community is fully engaged, and individuals comply with and participate in confinement measures and adequately use personal protective equipment. There needs to be global solidarity towards test access, and, importantly, infection control and diagnostic interventions need to be strongly intertwined to optimally combat current and future pandemics. Diagnostics should guide the choice of therapy and follow-up of therapy success.

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