Providing a laboratory diagnostic service for pandemic SARS-CoV-2 in a developing country

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Introduction

Coronavirus 2019 (COVID-19), caused by SARS-CoV-2, has spread rapidly after its emergence in China in December 2019 to cause a pandemic. Malaysia, a middle-income country in Southeast Asia, reported its first case on 25 January 2020. As of 28 May 2020, Malaysia had 7629 confirmed cases with 115 deaths. Real-time PCR diagnosis of SARS-CoV-2 with a fast turnaround time is an essential element of the pandemic response. Our teaching hospital in the capital city of Kuala Lumpur was the third site after the two national reference centres to offer PCR diagnostics, starting in late January. We would like to share our experiences from the perspective of a SARS-CoV-2 laboratory in a developing country.

Immediate issues

The initial issues in introducing the new PCR assay were the lack of a positive control and a 2 week delay in obtaining primers and probes from WHO-recommended protocols, as these are synthesised overseas. Fortunately, as part of a research grant on agents of respiratory infection, we had RNA from inactivated SARS-CoV. We shared this positive control with other laboratories until samples from newly diagnosed COVID-19 cases became available. This was an early illustration of the benefits of cross-talk between different organisations. The need for staff training was identified early; most of our existing molecular testing is fully automated with premixed reagents, which poses quite different challenges compared with a large-scale, fully manual extraction and PCR process for highly critical samples with a 24 h turnaround. In anticipation of a prolonged period of demand, we quickly expanded the pool of trained staff, redeploying technologists from less busy units. We developed a rota and workflow for the new SARS-CoV-2 test, and optimised it as new assays and equipment were incorporated and the workload grew.

We were fortunate that aggressive containment measures by the Ministry of Health kept the number of cases in the first month to 22, despite heavy traffic from China and Singapore, which had many cases in the early phase of the pandemic. This bought us valuable time to prepare for Malaysia’s main wave of infections, which started on February 27.

Shortages

An inventory of necessary items for testing was compiled and generous estimates of future needs were made. In anticipation of shortages through normal supply routes, calls were put out through social media to the hospital and university’s extensive network of contacts. This yielded valuable contributions from sometimes unexpected sources. For example, there was an early shortage of flocked swabs needed for sampling for PCR. Through a gynaecologist from the hospital, several thousand flocked swabs were obtained from a non-government organisation that carries out cervical screening for human papillomavirus. This supply tided the hospital over until a new supply of swabs arrived weeks later.

From an early stage, reagents and disposables from established European and American brands which we normally use became extremely difficult to obtain due to escalating global demand and unfavourable prioritisation of developing countries, leading to shortages coupled with higher prices. Suppliers were unable to fulfil their promised deliveries. This meant, for example, that our existing automated RNA extraction instrument, which requires extraction kits of the same manufacturer, was barely used. We switched to manual extraction of RNA, which became
the critical bottleneck in the high-volume demand for testing. The WHO-recommended primers and probes also ran out, and synthesis in the USA by our normal supplier was going to take many weeks.

At this point, we were being inundated with offers to supply extraction and PCR kits from local and regional (Asian) manufacturers. We filtered these offers using three questions: Is this kit approved for emergency use by the originating country’s regulatory body for medical devices? What is the cost? And is it quickly available? Some countries made their list of authorised assays available on the internet, which was very helpful. Effort was required to weed out offers from profiteers and manufacturers of lesser (or unknown) repute, as there is a real danger of substandard or fake items during shortages.\(^3\) We finally settled on several reagent sources from Korea, Malaysia, Singapore and China, which on evaluation were found to be cheaper and equivalent or better in performance to established Western brands. We were also fortunate that our geographic location in Asia meant strong existing distribution networks were in place with regional suppliers.

We decided early on not to depend on a single extraction or PCR kit, or a single supplier. Supply could be unpredictable; in one case, a manufacturer was prevented by their government from exporting the reagents we had already paid for, as the epidemic had worsened in that country. On occasion, our shipments were delayed by customs in transit for unknown reasons. On another occasion, one commercial PCR assay was found to miss 10% of positive samples; this was shown eventually to be due to primer site mutations which were unique at the time to Malaysian strains of SARS-CoV-2. The temporary loss of that particular assay reduced our available stock to one day’s worth of tests going into a weekend, necessitating frantic borrowing from other laboratories. We were fortunate that the manufacturer had been monitoring user reports and publicly available viral sequences, including some that we generated,\(^4\) so that they quickly identified the issue and provided new primers within a week. This shows the importance of selecting manufacturers of repute and of the importance of sequencing local strains. It also shows the potential risk of using a single gene target for screening during an evolving epidemic and highlights the importance of close communication with requesting clinicians to discuss unexpected results. This may be difficult when a laboratory provides diagnostic services for distant sites. The network of laboratories was valuable as it allowed sharing of reagents, evaluations of assays, troubleshooting advice and words of encouragement.

To monitor performance of the several assays we use, we carry out internal comparisons and participate in an external quality assessment scheme. There is also a useful regular review of whole genome sequences on GISAID (Global Initiative on Sharing all Influenza Data, www.gisaid.org), which includes a report of frequency of mutations in WHO-recommended primers regions.

Medical Device Authority and customs to facilitate delivery of necessary items. Donations from generous Malaysian people and organisations significantly supplemented the emergency government funding we received. As a semiautonomous statutory body, we were not subject to centralised procurement and thus were relatively flexible and nimble in dealing with different suppliers in an uncertain market.

It is vital to maintain laboratory staff health and morale. We instituted daily health screens for symptoms of respiratory infection and early referral to occupational health. We arranged the staff into teams who would have minimal contact with each other, so that in the event of a COVID-19 case within the laboratory, the impact from medical leave and compulsory quarantine on diagnostic services would be minimised. Ample food and refreshments were provided by donors, especially for those working extended hours. Laboratory technologists may become removed from the clinical implications of testing, as they become focused on completing laboratory procedures on hundreds of numbered samples. We therefore tried to maintain motivation and engagement by explaining with presentations and frequent reminders the critical role of laboratory testing, and how results inform major public health and hospital infection control decisions.

**Future perspectives**

Although Malaysia is currently seeing a decline in cases, we are prepared for continuing high demand in the short and medium term. Laboratories should also invest for the long term, as it is highly likely that SARS-CoV-2 testing will become routine. Suitable equipment, facilities, reagents and human resources are needed to strengthen molecular diagnostics in as many laboratories as possible, as well distributed throughout a country as possible. Inter-ministerial efforts are needed to coordinate laboratories from healthcare facilities (public and private), universities and industry who are able to contribute to national diagnostic capacity. A coordinated national testing capacity should also be able to respond quickly to help specific sites, which may be overburdened by a localised cluster.

Over-regulation of testing clearly delayed widespread introduction of laboratory testing in the USA.\(^5\) Regulatory bodies should therefore facilitate emergency use authorisation while at the same time ensure minimum standards of test evaluation and the results of evaluation available. Finally, Malaysia should consider developing manufacturing capacity to become self-sufficient in high-quality diagnostic reagents, to reduce reliance on imports. The COVID-19 pandemic has greatly challenged the chain of administrative and technical processes that lead to a final laboratory result. It should also be viewed as an opportunity to strengthen and extend existing laboratory networks for continuing and future threats.

**Administrative and human resource issues**

Administrative support is crucial in ensuring a smooth supply of reagents and equipment. Our centre had an efficient team who coordinated donations, negotiated with suppliers and couriers, and liaised with government bodies such as the treasury, the
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