COMMENTARY

Covid-19 preparedness and response: experiences of the Nigerian Institute for Medical Research

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SUMMARY

The global community is facing a health crisis caused by coronavirus disease 2019 (COVID-19). The coronavirus pandemic is severely disrupting the global economy. Countries are battling to slow the spread of the virus by testing, employing contact tracing, restricting travel, quarantining citizens, and encouraging use of face mask, hand hygiene and social distancing.
measures. The lockdown imposed in many countries including Nigeria has resulted in increased cost and shortages of reagents and supplies worldwide. Due to the highly contagious nature of the disease, rapid rate of spread, and lack of an effective therapy, it became necessary for nations of the world to mount an efficient response mechanism to curb the spread of the pandemic. The Nigerian Institute of Medical Research (NIMR) has responded actively to the current pandemic with some innovations with respect to sample collection systems, molecular diagnostics, kit development and validation. Due to the highly infectious nature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) the causative agent of COVID-19, the institute also invested in the production of infection control tools. The extent of response by the institute would not have been possible but for collaboration and partnership with well-meaning organizations and stakeholders. National, State and public cooperation are very essential for effective response to any pandemic. The response of NIMR to the pandemic is herein discussed. Lessons learned and recommendations made are also shared to help institutions interested in combating this and future pandemics of similar nature.

Key Words: Pandemics, preparedness, COVID-19, response

ISSUES
The global community is facing a health crisis caused by a pandemic due to coronavirus disease 2019 (COVID-19). Pandemics have been a part of human history but the most fatal recorded was the Black Death, also known as The Plague. It killed between 75-200 million people in the 14th century (1-3). Other major pandemics recorded include the Plague of Athens, which occurred between 430-426 BC. It occurred during the Paloponnesian war and claimed about two-thirds of the Athenian population (4). Since then, there have been several other pandemics globally, including the Antonine plague of 165 AD which killed five million (5), Cyprian plague of 251 AD killed 5,000 people a day in Rome and the Justinian plague of 541 AD claimed 10,000 lives a day (6) resulting in the death of about half the human population of the then world (7).

A pandemic is a sudden occurrence of an infectious disease with a worldwide geographic spread affecting a high proportion of the population with sustained person to person transmission. Additionally, it has a very high death toll with devastating effects because it is usually caused by a new organism against which the infected persons have no immunity. The Spanish flu of 1918-19 was one of the deadliest pandemics. It was reported to have killed at least twenty million people, more than twice the number killed in the military action in World War 1 (8). Nigeria also witnessed the Spanish Flu pandemic caused by Influenza virus, which claimed about 500,000 lives of the 18 million Nigerian population in less than six months (9). It spread fast and wide without much difficulty and, 50-80% were stricken by the virus. Some pandemics, which have occurred in 21st century, include the H1N1 pandemic of 2009 which caused no fewer than 300,000 deaths and the SARS pandemic of 2003 which infected 8,096 people from 27 countries and claimed 774 lives (10). Currently, the pandemic ravaging the world is COVID-19. This disease caused by SARS-CoV-2, originated from Wuhan, China in December 2019 and it has spread to 213 countries globally with 6,875,191 confirmed cases and 398,689 deaths as of June 6, 2020.Africa has confirmed 179,997 cases with 4,954 deaths while Nigeria, third most impacted in the continent confirmed 11,844 cases and 333 deaths as of June 6, 2020 (11).

Generally, pandemics spread rapidly around the world, posing enormous health, economic, environmental and social challenges to the entire human population. The coronavirus outbreak is severely disrupting the global economy. Countries are battling to slow the spread of the virus by
testing and treating patients, employing contact tracing, restricting travel, quarantining citizens, and cancelling large gatherings such as religious meetings, sporting events, concerts and schools in other to ensure social distancing. The pandemic is spreading fast with more severe effects on the aged and persons with underlying health conditions. COVID-19 is much more than a health crisis; by stressing every one of the countries it touches, it has the potential to create devastating social, economic and political crises that could leave deep scars (12). Due to the severe impact that pandemics could have, it is important that health allied agencies respond effectively to mitigate their impact. The response to COVID-19 by the Nigerian Institute of Medical Research (NIMR) is herein discussed.

**DESCRIPTION**

**Molecular detection and sequencing of SARS-CoV-2**

NIMR has a mandate to research into communicable and non-communicable diseases of public health importance in the country. In her quest to accomplish this mandate, the institute collaborates with other institutions within and outside the country. It was such collaboration with China Center for Disease Control that paved way for two of our staff to attend a three-month training program in China on Molecular Diagnosis and Pathogen Identification Techniques for Emerging and Reemerging Infectious Diseases. The aim of this training was to improve laboratory capacities of the participants in conducting molecular detection assays and implementing molecular diagnosis for potential pathogens associated with emerging and reemerging infectious diseases. The training also had an objective of developing leadership in scaling up capacity in the home countries of participants. Our staff was away from July to September 2019 and upon return, they had acquired skills for:

- Development of fast point of care PCR panels for febrile illnesses
- Design of primers for prompt identification and diagnosis of arboviruses and other viruses of interest.
- Targeted and whole genome sequencing and designing of the primers needed for them.
- Discovery of viruses and other pathogens using next generation sequencing (NGS)
- In house production of enzyme linked immunosorbent assay (ELISA) kits

Similarly, three other staff were at the Institute Pasteur, Dakar, Senegal between September and October 2019 to acquire more skills on the use of NGS and detection of viruses using in-house serological assays. Upon their return from the training, a viral surveillance team was set up in November 2019 to harness the skills they had acquired in preparation for any viral outbreak in the country. The team met biweekly to set up plans, and design assays in preparation for any eventual viral outbreak. Purchase orders were placed; primers and probes were designed and purchased. One of the Chinese collaborators visited the institute in January 2020, at the onset of the coronavirus outbreak in Wuhan, China. It was then agreed that some qPCR kits be obtained for diagnosis of COVID-19 in Nigeria. At that time, we designed primers and probes specifically for conventional PCR and sequencing of beta coronavirus. By February 2020, some companies in-country requested to screen their Chinese workers returning from their lunar festival for SARS-CoV-2, before commencement of work. This service was provided with ease as we were prepared for it. The management of the institute formally informed the Honourable Minister of Health of Nigeria of our preparedness to respond to the pandemic in the country. As soon as the index case was detected, an aliquot of the extracted RNA and a COVID-19 blind panel from Nigeria Center for Disease Control were sent to NIMR to confirm our laboratory readiness for the response. The samples were successfully tested at the Center for Human Virology and Genomics (CHVG) on...
February 28, 2020 and we proceeded to sequence the index case using the Sanger sequencing technology (13). The institute has since deposited some partial and full-length genome sequences in the GenBank (Accession nos. MT159778; MT344135). Subsequently, CHVG was included in the network of COVID-19 testing laboratories in Nigeria.

In addition, the institute supports the Lagos State Biobank with testing of samples collected from their decentralized sample collection centers. CHVG has access to three qPCR machines and a COBAS 6800 (Roche) system, which together can generate 700 test results daily, if fully optimized. In addition, the Center for Tuberculosis Research (CTBR) in NIMR, currently has three GeneXpert machines, has been designated for COVID-19 testing in Lagos state. The CTBR is on standby for activation for COVID-19 testing any moment from now. As of June 6, we have tested >6,000 samples with results all issued out. Furthermore, CHVG has provided some back-up testing support to other laboratories in the COVID-19 network.

Establishment of the first drive-through sampling centre in Nigeria
The institute with the support of one of her partners, Life Bank, established a modified drive-through center (submitted for publication) where samples are collected daily for testing. Many persons register daily on our website (https://nimr.Covid.com.ng/) to access COVID-19 diagnosis through our drive through center. However, we are unable to invite all of them to the facility because only about 150 persons can be attended to daily. Consequently, we had to introduce another innovation to meet the demand using telemedicine approach in collaboration with Mobilhealth International. This is a self-sample collection model to increase access to COVID-19 testing in the institute. This approach minimizes person to person contact presently being experienced at the modified drive through sample collection center.

COVID-19 research at NIMR
Development of point of care (POC) diagnostic assays
As testing services were being provided, research was also prioritized in line with our mandate. In anticipation of stock out of test kits due to the global demand for same reagents, we embarked on the development of in-house assays that can be deployed for field and laboratory use to control the pandemic. Primers and probes for detection of SARS-CoV-2 using qPCR were designed and are being evaluated and optimized. Earlier, NIMR had developed a DNA extraction kit. Subsequently, an RNA extraction kit suitable for COVID-19 was developed and is presently being validated.

The institute also adopted another approach for the development of rapid, sensitive, and specific nucleic acid testing platform for diagnosing SARS-CoV-2. This is an isothermal point-of-care (POC), field test system developed by our staff as part of skills acquired, during the training in China. This POC platform was utilized to develop sensitive multiplex PCR diagnostic assays for febrile illnesses. In six tests, these febrile illness assays differentially detect the top 10 causes of febrile illness in children, including malaria (Plasmodium falciparum), typhoid Fever (Salmonella enterica serovar typhi and paratyphi), Streptococcus pneumoniae, Brucella abortus, Leptospira interrogans, Dengue 1-3 viruses, yellow fever virus, rotavirus A and chikungunya virus. These assays are presently being validated and field tested. Subsequently, this technology and platform is being used to develop multiplex qPCR assay for diagnosing SARS-CoV-2 and Influenza A virus in one test. Currently, the assay primers and probes have been synthesized and received in the laboratory. Also, isothermal reagents and equipment for pilot testing have been purchased.

Other plans to develop rapid diagnostic tests (RDT), enzyme linked immunosorbent assays (ELISA) and candidate vaccines are still at the initial phase of development.
Evaluation of commercially available rapid diagnostic tests (RDTs)
Several RDTs and ELISA kits have flooded the country seeking for evaluation. The CHVG is a WHO prequalification evaluation laboratory with long experience in validation of molecular and serological test kits. Thus, RDTs and ELISA assays are being validated at the CHVG to determine their performance characteristics on behalf of the National Agency for Food and Drug Administration and Control. Results obtained guide in determining their approval for registration in the country. Several other COVID-19 related research projects embarked upon at NIMR include, amongst others, nationals ero-epidemiological survey, co-morbid infections associated with COVID-19 and clinical trial of the safety and efficacy of chloroquine phosphate, hydroxychloroquine sulphate, Azithromycin, and lopinavir/ritonavir for treatment of COVID-19 in the country.

Production of infection control materials
The lockdown imposed in many countries of the world, with attendant economic stagnation has resulted in increased cost and shortages of reagents and supplies globally. It is said that “necessity is the mother of invention”. As such, NIMR has looked inward to generate infection control materials required to combat the pandemic. We have within CHVG, developed a standard protocol and began production of hand sanitizers and decontamination solutions for the entire institute. As a matter of fact, a private company has entered into an agreement with the institute to supply the hand sanitizers commercially for public use. In the same manner, face masks produced in bulk by another company are sent to NIMR where they are sterilized using UV rays and packaged for public use. Prior to this pandemic, the institute had two tissue culture laboratories, which produced viral transport medium (VTM) to maintain cell lines. At the nick of time, when VTM became a scarce commodity in the country, the laboratories began commercial production of VTM for use in sample collection at the national and state levels as well as for some private organizations. All these ventures became some source of revenue for the institute. So, while the pandemic was taking its toll in the country, we were discovering our strengths for improved productivity.

Biosafety procedures at NIMR
At the onset of the pandemic, a risk assessment was conducted within the three centres in the microbiology department of the institute. A standardized template from WHO website was used and gaps identified were closed. All technical staff interested in the response undertook the WHO infection prevention control training for COVID-19 and their certificate of training was a requirement to enrol in the response. Additional trainings, such as doffing and donning of PPEs and preparation of decontaminants were also conducted. Non-technical staff such as storekeepers, security personnel, clerical staff on the team were also provided relevant trainings’ to ensure their protection. A daily log for COVID-19 symptoms was deployed to all staff to monitor early signs of infection; this was to help early detection of COVID-19 infection and to prevent transmission amongst our staff. Some essential staff were lodged in a research suit within the institute to minimize contact with their families in order to prevent infection. Furthermore, staff were encouraged to test at intervals when they had suggestive symptoms or before visiting their families.

We adopted the modified drive through centre because it is noted to protect health care workers from infection. A drive through sample collection centre has an advantage of reducing contact and exposure time, thus reducing risk of infection transmission to health care workers and clients (14). Even though WHO recommends Biosafety Level 2 (BSL-2) for non-propagative diagnostic laboratory work like sequencing and nucleic acid amplification test (15), since the institute has a
biosafety level 3 (BSL3) laboratory, all samples received for testing are inactivated in the BSL3 laboratory before further processing in the BSL2 laboratory.

LESSONS LEARNED
Top leadership involvement and investment in training
There is a saying that “success is where preparation and opportunity meet”. This is what describes our response. This explains why the institute invested in training her staff in foreign countries. The knowledge gained was also harnessed into productive use. When the opportunity came knocking, the institute was ready to respond. One major strength that facilitated the strategic and prompt response from the institute in combating the raging pandemic is the dynamic leadership style of the top management. The involvement of the top leadership was very apparent, solutions and suggestions were provided for challenges that came along the way. Staff were encouraged to think outside the box to break new grounds. Established protocols had to be circumvented in order to make progress. A response team was set up with personnel drawn from different departments within the institute and some volunteer staff were engaged. A reporting structure was put in place and the team went straight into action with review meetings held twice weekly. The commitment of the top management was quite motivating, and this reinforced team work among the staff. All staff worked hard and long in response to the pandemic. Some staff got infected in the course of work, were admitted in different isolation centers in Lagos, recovered, were discharged and have resumed work. Despite this experience, the staff were not deterred; they are still willing to lay down their lives to fight the pandemic. This is without any commitment to remuneration nor promise of hazard allowance. This uncommon gesture is worthy of emulation by other Health Care Workers.

Collaboration and partnership
The extent of response by the institute would not have been possible but for the collaboration and partnership with well-meaning organizations and stakeholders. It was the collaboration with the China Center for Disease Control to foster Africa Public Health Cooperation that enabled our staff training. Similarly, in December 2018, the institute had signed a memorandum of understanding with the Institute Pasteur, Dakar, Senegal to foster south-south collaboration to birth new feats in the field of research in the west coast region. This was what led to the opportunity for the training of some of our staff in 2019. Other non-governmental organizations that partnered with the institute include LifeBank that supported the establishment of a drive through testing center, provision of personal protective equipment (PPE) and bore some other expenses. Co-creation Hub Nigeria maintained the COVID-19 testing link on our website. Mobihealth anchored the self-sample collection innovation with their online application. Other organizations that supported the response in NIMR include Nigerian LNG limited, which supported with purchase of some reagents, Flour Mills, Nigeria Plc and AL Samparda Pharma Nigeria Ltd donated PPEs and other consumables required for the response. The goodwill we enjoyed from the electronic and print media also helped to facilitate our response.

Effective response to future pandemics
COVID-19 is still here with us. Research is in progress for the development and evaluation of effective therapeutic agents for treatment and vaccines for prevention of COVID-19. Meanwhile, concerted efforts must be directed at increased testing, contact tracing, isolation and non-therapeutic measures to contain viral spread. While COVID-19 may be reduced or eliminated at some stage, another deadly pandemic is likely to occur again, although it will be difficult to predict
exactly when the next one will be. As the years go by, pandemics will become more frequent because of increased and unprecedented rates of human travels and other interactions with nature. A multi-disciplinary approach to problem solving will be required for adequate preparation and effective response to future pandemics, including identification and evaluation of herbal products and their potential roles. The 21\textsuperscript{st} century pandemic response approach will need to be multifaceted and integrated cutting across several subject areas and disciplines such as, governance and infrastructure, engagement and communication, social sciences including anthropology and human geography, emerging technologies (pathogen genomics, data science, and artificial intelligence). Other subject areas include research and development that go beyond epidemiology to include, diagnostics, therapeutics and vaccine development, one health that connects human health to animal health and the environment and, ethical considerations requiring consent and innovative and adaptive clinical trial designs (16). Surveillance that is systematic, simple and consistent will be required for data aggregation and trend monitoring. Data quality and dissemination plans are also crucial attributes in this process. Modelling for prediction and forecasting will be necessary as well as implementation research that are aimed at turning basic research findings into health-improving products.

RECOMMENDATIONS
National, State and public cooperation are very essential for effective response to any pandemic. Because pandemic is a global problem, health diplomacy and collaboration with major global health institutions such as the World Health Organization is also crucial. Enhancing trust and cooperation, between people, regions, states and the federal government is paramount for a sustained fight against the pandemic (11). It is therefore important to work in collaboration with both the states and federal government in combating the pandemic. The Nigeria Center for Disease Control supplied some kits, reagents and consumables required for testing while Lagos State Ministry of Health posted surveillance officers to the institute to work with the team. They completed case investigation forms for each client that visited and uploaded our results to the state and national database. They ensured infected persons from our testing center were evacuated and admitted in the isolation centers. Therefore, in conducting the COVID-19 testing, it is essential to collaborate with the appropriate authorities.

However, it is also essential that staff remuneration and hazard allowances are settled by the appropriate authorities as this will help sustain enthusiasm of the staff. This is especially important as it relates to a highly infectious agent as SARS-CoV-2, which is infecting health workers daily despite their boldness in combatting the pandemic. Infection control measures need to be at its maximum in combating this and other pandemics (17, 18). It is essential that adequate personal protective equipment (PPE) is provided for frontline staff, and training on infection prevention and control is very essential. Preventing staff burn out is also very critical, as work intensity and inadequate rest may make them prone to infection (19). The importance of these measures cannot be overemphasized.

Since the COVID-19 outbreak, the global supply chain for PPE and relevant test kits and reagents has not adequately functioned to meet the surge in demand. Constraints in supply and logistics, including export bans for PPE and key materials, have become an unpleasant reality (20). It is, therefore, important to encourage indigenous production of PPE materials, kits and supplies for national use. The government and private sector should invest in purchase of essential equipment like the oligo synthesizers to facilitate local production of relevant primers, probes and kits for diagnostic use in the country, and automated sample nucleic acid extraction systems. Grants
should be awarded for such production ventures and the outcome of such will indeed lead to research and development for national growth. This pandemic thus provides an opportunity for national development and this opportunity should be fully utilized to the benefit of the country because future pandemics are bound to be more frequent than they have ever been.

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