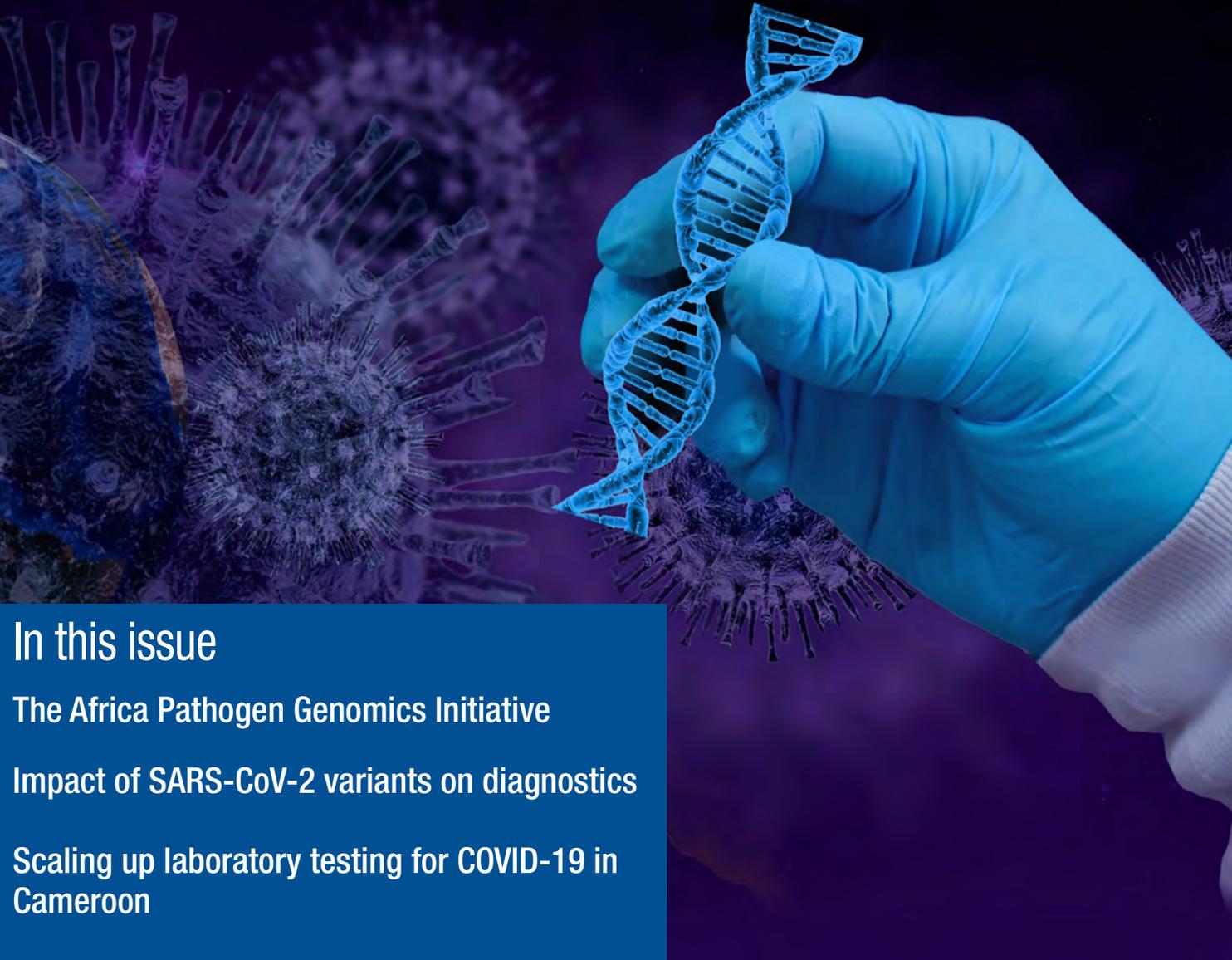




LAB CULTURE

ADVANCING THE LABORATORY PROFESSION AND NETWORKS IN AFRICA

Pathogen genomics: A powerful emerging tool for disease surveillance and outbreak response in Africa



In this issue

The Africa Pathogen Genomics Initiative

Impact of SARS-CoV-2 variants on diagnostics

Scaling up laboratory testing for COVID-19 in Cameroon



LAB CULTURE

March 2021 | Issue 25

ADVANCING THE LABORATORY PROFESSION AND NETWORKS IN AFRICA

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Contribute to *Lab Culture*

ASLM is currently accepting article and photo submissions for upcoming issues of *Lab Culture*. We publish timely, informative, inspirational articles relevant to the unique challenges faced by laboratories in resource-limited settings. We are interested in articles on the critical aspects of laboratory medicine, best practices, success stories, leaders in the field, industry news, etc.

To submit article or photo proposals, please contact the Editor at newsletter@aslm.org.

Lab Culture. Established along with ASLM in 2011 as a member newsletter, *Lab Culture* relaunched in 2017 as ASLM's magazine for laboratory medicine in Africa. Dedicated to bringing timely, informative articles relevant to the unique challenges faced by African laboratories, *Lab Culture* seeks to be Africa's premiere resource for laboratory professionals and other stakeholders working on with the continent. Published six times a year as a digital edition, *Lab Culture* includes features on critical aspects of laboratory medicine and best practices in resource-limited settings, success stories from the continent, industry news, and more.



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Pathogen genomics: the future of surveillance in Africa

It is now more than a year since the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) to be a pandemic threat. Since then, Africa has recorded 4 005 204 cases, 107 001 deaths and 3 589 067 recoveries, representing 3.6% of global cases. Since the beginning of the epidemic, the African continent has scaled up its capacity to detect the virus, within the 55 member states using reverse transcriptase-polymerase chain reaction (RT-PCR) tests and progressively implementing antigen rapid detection tests to further increase access to diagnostics.

Recently, a new challenge has emerged in the form of new variants of severe acute respiratory coronavirus 2 (SARS CoV-2) identified in the United Kingdom, South Africa and Brazil. Genetic variability is a normal feature of viruses, providing them with opportunities to adapt to the environment. Changes of the viral RNA or DNA can confer new characteristics, such as the ability to escape treatment, become more virulent or become invisible to laboratory detection techniques.

Monitoring the emergence of new variants and understanding the significance of mutation(s) to transmission, treatment, and vaccine response is key to staying ahead of the pandemic and requires new tools. Pathogen genomics is an area of biomedical science that

studies the DNA/RNA sequence of microorganisms. It allows us to understand the functions behind the genes, without having to culture live organisms in a laboratory, and investigate where these organisms come from through their relationship with each other. Next generation sequencing offers the possibility to study pathogens in greater detail and much quicker than the classical Sanger sequencing method.

Using these techniques, South Africa swiftly identified the SARS-CoV-2 B.1.351 variant, documented its faster transmission rate and anticipated the possible decrease of effectiveness of the Oxford University AstraZeneca vaccine in preventing mild and moderate forms of COVID-19. Prof Tulio de Oliveira, whose institute KRISP (South Africa) contributed to this investigation, says, 'If we work together and if we have access to high-tech technology, we can be leaders in the world of genomic surveillance'. In this particular case, Africa has been ahead of most nations, illustrating that, provided with the right tools, the continent can lead relevant research informing public health decisions globally.

The new SARS CoV-2 variants have highlighted the need for incorporating more pathogen genomics information into the public health decision making process. Increasing the availability

of representative, good quality pathogen genomics data without disrupting the scale up of COVID-19 diagnostic and other essential health and testing services requires coordination and partnerships at continental, regional and national level. The Africa Centre for Disease Control (CDC) is stepping up alongside other stakeholders like WHO to shape the African agenda. The strategy is to start by leveraging existing capacity in laboratory centres of excellence conducting pathogen genomics in support of control programmes for HIV, malaria, tuberculosis or antimicrobial resistance.

In this issue of Lab Culture, Africa CDC highlights its plan to support genomic surveillance of SARS-CoV-2 through the Africa Pathogen Genomics Initiative. The role of pathogen

genomics for public health is further unpacked by Prof Christian Happi, a molecular biologist and genomics expert from the African Center of Excellence for Genomics of Infectious Diseases in Nigeria. The Foundation for Innovative New Diagnostics explores the impact of SARS-CoV-2 variants on current diagnostic testing practices. Sharing a unique field implementation perspective, the Centre Pasteur de Yaoundé describes the Cameroonian journey towards the scale up of COVID-19 testing. Maintaining a focus on other essential testing services, Dr Christopher Maske of QLAB Laboratory in South Africa reviews how assay design and performance can improve human papillomavirus screening initiatives and reduce the incidence of cervical cancer in Africa.

ERRATA

Issue 24, Page 2 and Pages 13-14:

In the Table of Contents for Issue #24, the article about Patience Dabula was misidentified as a Q&A article. This article should have been labelled as a Leaders from the Bench article both in the Table of Contents and on pages 13-14.

Issue 24, Page 2 and Pages 15-17:

In the Table of Contents for Issue #24, the article by Patrick Mateta "What is the difference between quality control, quality assurance, external quality assessment and quality management system?" was misidentified as a Feature Topic article. This article should have been labelled as a Q&A article both in the Table of Contents and on pages 15-17.

The editors of Lab Culture sincerely apologise for these errors and any confusion that may have resulted



Collins Otieno, PhD.
African Society for
Laboratory Medicine

What is genomics?

ASLM recently sat down with Dr Christian Happi of Redeemer's University in Nigeria to get his insights on genomics and its importance to disease control.

What is genomics, and what is the difference between genomics and genetics?

Genetics is the study of individual genes, functions and effects. While genomics is the study of all the genes (genome) of an organism. That is, genomics looks at all the genes of an organism and how they interact.

What are some key applications of genomics for disease control in general?

Genomics contributes directly to the development of diagnostics, therapeutics, and vaccines, all of which are important disease control tools. Taking the pandemic as an example, without the genomic data of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it would have been difficult to develop coronavirus disease 2019 (COVID-19) diagnostics, therapeutics and vaccines.

Also, the pandemic illustrates how genomics accelerates all public health disease control tools. Within a year we went from knowing nothing about the virus to understanding its genome and on to developing diagnostics and vaccines for it. That emphasises the fire-power of genomic knowledge and how it can facilitate public health response, while accelerating science in so many ways.

Genomics can also help guide public health interventions. A case in point is the response to SARS-CoV-2 in South Africa, where genomics helped to identify new strains of the virus. Before that, during the 2014-2016 Ebola virus disease outbreak in West Africa, genom-

ics was used to develop diagnostics in response to the outbreak and the genomics data were made open access, so other researchers could use them. Both of these examples from different outbreaks demonstrate how powerful it is to interface genomics-based tools and their outputs with the public health response.

The two major things to remember when it comes to infectious disease outbreaks are the importance of speed and accuracy. These are exactly the two major things that genomics offers.

What are some of the COVID-19-related questions that genomics can help to answer?

Genomics not only provides an understanding of the origin, spread and evolution of the SARS-CoV-2 but also gives deeper insights into community transmission. For example, epidemiology can only tell that person A got infected from person B. Genomics adds not only scientific evidence that person A and person B are both infected with the same virus, but can also show that new lineages are emerging and determine whether such lineages are independent events, linked to another transmission chain or were imported. All of that information helps to guide public health authorities with how to manage response during a pandemic.

Why is it important to scale up genomics capacity on the African continent?

Genomics has huge potential to contain and prevent infectious disease outbreaks, especially in Africa, which is regularly at the centre of such outbreaks. More than 70% of pathogens with pandemic potential emerged from Africa. It is very difficult to identify such pathogens using only conventional microbiology or virology. Genomics offers the ability to do surveillance in near real-time, enabling

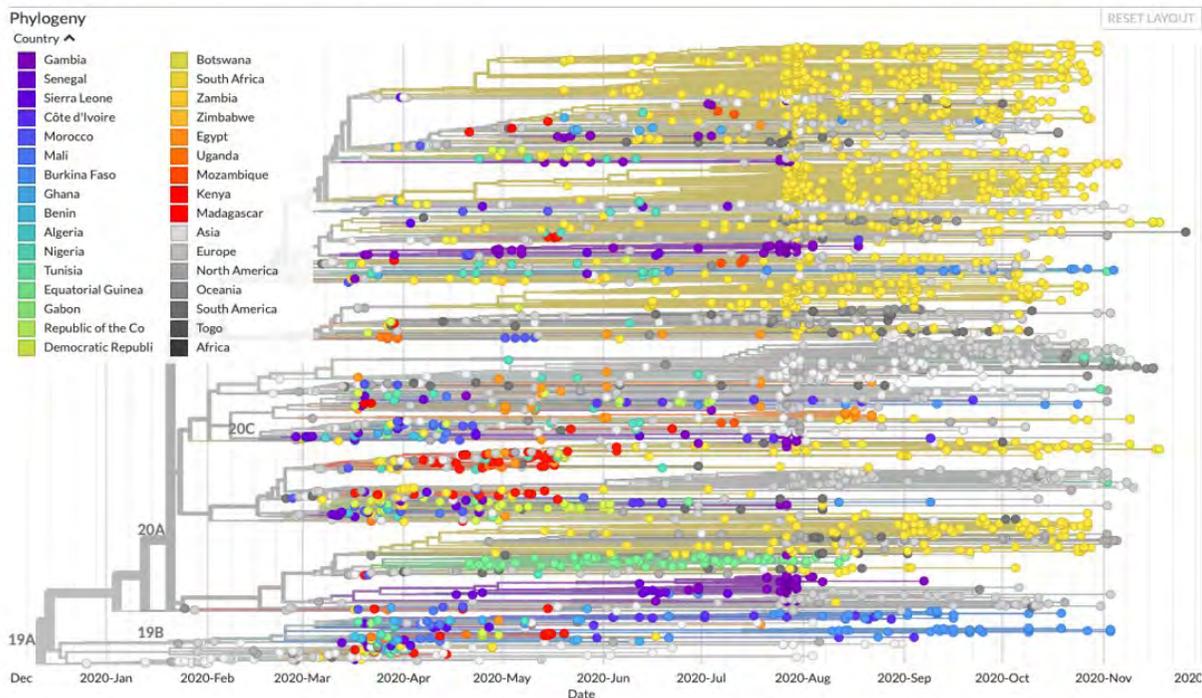


Christian Happi, PhD
Redeemer's University
Nigeria

Genomic epidemiology of novel coronavirus - Africa-focused subsampling

Maintained by the Nextstrain team. Enabled by data from [GISAID](#)

Showing 3216 of 3216 genomes sampled between Dec 2019 and Nov 2020.



Nextstrain phylogeny of SARS-CoV-2 genomes from Africa and selected global genomes

early identification or discovery of pathogens.

An example of 'pathogen discovery' is the work my group did on Lassa fever.¹ We wanted to understand the drivers of unexplained acute febrile illness in which patients presented with classic signs of Lassa fever, but patients all tested negative for the virus. In the first application of genomics in Africa, we discovered in these patients two brand new rhabdoviruses, which were similar to a virus described in DRC in 2012 and associated with hemorrhagic fever.

Genomics can also uncover disease outbreaks that conventional epidemiology misses. In 2018, a cluster of school-aged children in Edo State Nigeria was dying of an unexplained illness, and conventional diagnostics that tested for Lassa, Ebola and yellow fever were all negative.² Within 48 hours of samples being sent to our laboratory, results showed the cause as two strains of yellow

fever so different from those that had been circulating in Nigeria over the past 92 years that the current diagnostics missed them. This information was made available to Nigerian public health authorities, who declared a Yellow fever outbreak, and we were able to contain the outbreak within two weeks.

Scale-up of genomics capacity gives Africa the power to be ahead of the curve with public health responses to outbreaks. The ability of genomics to identify existing and discover new pathogens, characterize them, and develop countermeasures against them, before they spread widely means many lives will be saved.

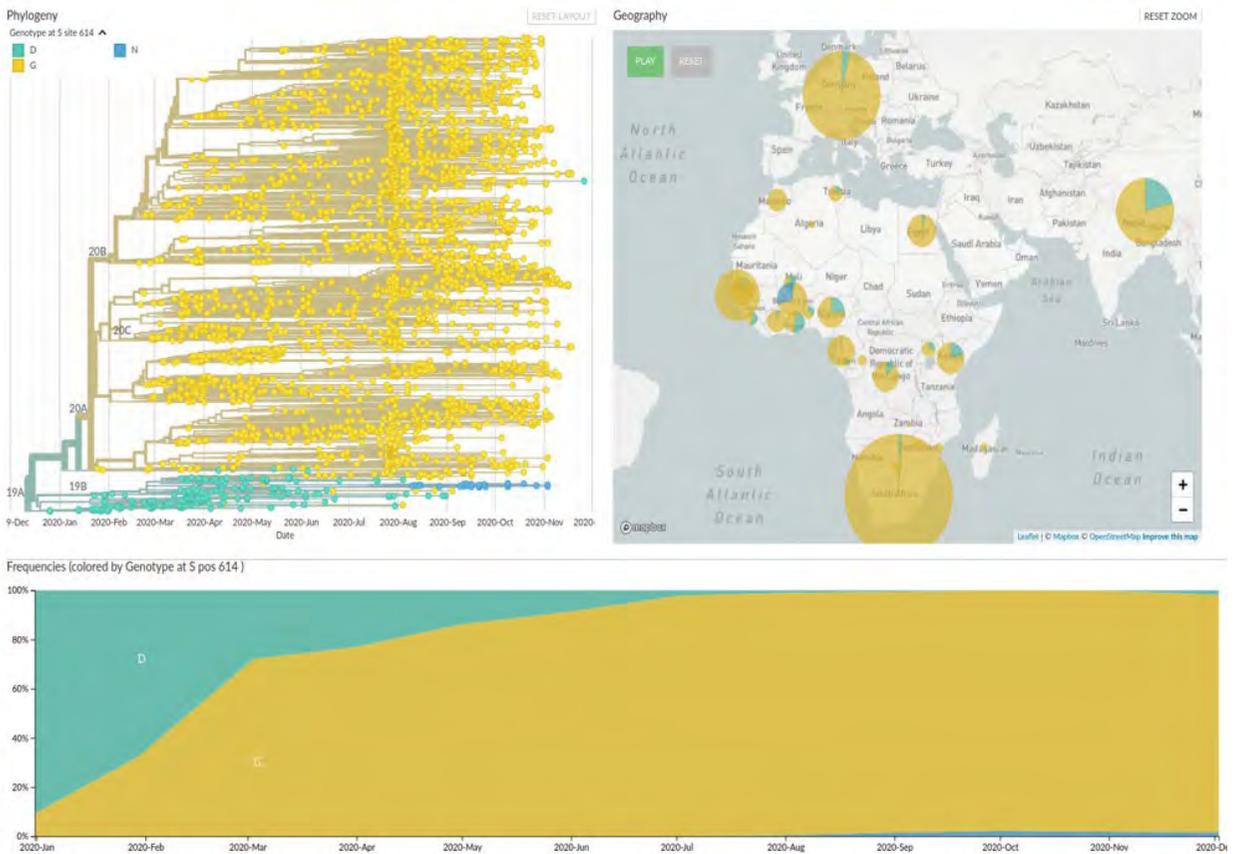
What are the challenges and opportunities when implementing pathogen genomics networks in Africa?

One of the many challenges to implementing pathogen genomics networks in Africa is that countries

are not open to cooperation and collaboration. Currently, there are too many 'silos', in which knowledge, technology, expertise, etc. are sequestered and unavailable beyond the local context. To overcome this, Africans must leave aside politics, nationalism, pride and sentiment, so technologies can be accessed for a better public health system.

Another challenge lies in the supply chain. Ensuring a constant flow of reagents and supplies is essential, but faces many barriers, such as customs and import delays. The production of reagents and supplies on the African continent would help, because most countries are very dependent on supplies from the West, i.e., Europe and North America.

Opportunities for the implementation of pathogen genomics networks abound. First, Africa must leverage existing facilities to increase its ability to respond to disease outbreaks. Specifically, existing facilities



The D614G mutation is influenced by a substitution mutation of nucleic acid A to G at position 23403. The proportion of this mutation in the spike protein in Africa is shown above (2028 African Genomes)

can be utilized to help countries that do not have the resources to address public health challenges. Second, existing facilities and expertise should be directed towards building a critical mass of well-trained African scientists that can use their skills and knowledge to help the public health response in their countries. The goal is to create a system within Africa that can help the continent as a whole to respond effectively.

The ability of South Africa to respond to the COVID-19 pandemic much faster than countries in the West is one example of already existing capacity that can be leveraged. Another example is the ability of Nigeria to publicly share the whole genome of the first COVID-19 case in the country within 48 hours. That kind of speed was not matched anywhere else in the world. These examples show that there is no reason why Africans should not

be the ones leading the world. Although the technology needed to combat them comes from the West, outbreak-related pathogens and microorganisms are much more common in Africa. Thus, Africans should not just use technology and be the learners, but become the masters and the teachers.

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Citation

What is genomics?. *Lab Culture* 2021, No. 25, Pages 06-08.

Prof. Christian Happi is the Director of the World Bank-funded African Center of Excellence for Genomics of Infectious Disease (ACEGID), Professor of Molecular Biology and Genomics, and the former Dean of the College of Postgraduate Studies at Redeemer's University, Nigeria. He completed his PhD at the University of Ibadan, and his postdoctoral fellowship at Harvard University, School of Public Health. He received the Merle A. Sande Health Leadership Award in 2011; the 2016 Award of Excellence in Research, by the Committee of Vice-Chancellors of Nigerian Universities; the 2019 Human Genome Organization (HUGO) Africa Prize for his seminal work on infectious diseases genomics in Africa, including Ebola and Lassa fever and the 2020 Bailey K. Ashford Medal by the American Society of Tropical Medicine and Hygiene (ASTMH).

The Africa Pathogen Genomics Initiative

A continent-wide initiative to strengthen public health surveillance systems and outbreak preparedness

Introduction

Following recent advancements in sequencing technologies, a new field of disease surveillance termed 'pathogen genomics' has emerged. Pathogen genomics promises to enhance precision public health by enabling prevention and timely management of outbreaks and more effective control of endemic diseases.¹ In the first month of the current coronavirus disease 2019 (COVID-19) pandemic, scientists used genomics to determine that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal virus of COVID-19, was capable of human-to-human transmission, fundamentally shaping understanding of the disease and confirming its pandemic potential.

Genomic data were also used to guide the development of diagnostics and vaccines. Over time, scientists from around the world have published open-source SAR-CoV-2 genome data and analyses to further track the spread of the pathogen and inform critical response efforts, as well as monitor viral evolution.²⁻⁵ Scientists have been able to link the recent second-wave to the emergence of new variants that have high transmissibility, e.g., the 501Y.V1 (B.1.1.7), 501Y.V2 (B.1.351) and 501Y.V3 (B.1.1.28.1).⁶⁻⁸

Modelling studies show that these genomic variations increase the transmissibility of the variants by up to 75% compared to earlier circulating variants and may also impact diagnostics, therapeutics and vaccine development and deployment.⁹⁻¹¹ Using these data, countries can track the spread of the emerging variants and respond better to the pandemic, thereby minimizing their impact.

The Africa Pathogen Genomics Initiative

Besides COVID-19, the World Health

Organization recommends genomic surveillance as an integral tool in surveillance focused on elimination of vaccine-preventable diseases¹² and antimicrobial resistance,¹³ including HIV, tuberculosis and malaria drug resistance,^{14,15} as well as foodborne pathogens.¹⁶ Harnessing the benefits of genomics is vital to protecting and improving Africa's health security. Despite the falling costs and turn-around times of genomic technology and the greater need to rapidly manage outbreaks and control infectious diseases, this technology is not within reach for most National Public Health Institutes (NPHIs) on the continent.

In line with its potential epidemic preparedness mandate, the Africa Centres for Disease Control and Prevention (CDC) has been working to support NPHIs by strengthening capacity for disease surveillance and intelligence, laboratory and information systems, public health research and workforce development. To further accomplish this mandate, Africa CDC, in partnership with the Bill & Melinda Gates Foundation, the United States CDC, Microsoft, Illumina (a genome sequencing technology company), and Oxford Nanopore Technologies (a United Kingdom-based biotechnology company), launched the [Africa Pathogen Genomics Initiative \(Africa PGI\)](#) on 12 October 2020.¹⁷ Africa PGI, a four-year program, aims to strengthen the continent's disease surveillance by integrating genomics-sequencing technologies. This will enhance disease surveillance, prevention, rapid detection and response, as well as facilitate the control and elimination of endemic diseases.

The initiative has four major components:

1. Building a Pan-African network of genomics laboratories and Bioinformatics institutes



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Figure 1. Africa CDC-WHO SARS-CoV-2 genomics laboratory network

2. Developing the laboratory workforce
3. Creating enabling mechanisms to support sustainable genomics-based surveillance on the continent
4. Implementing genomics for priority use-cases

Building a Pan-African network of genomics laboratories and bioinformatics institutes

Africa PGI will capacitate more than 20 NPHIs with next-generation sequencers, data systems, mechanisms for quality assurance and build a continent-wide laboratory referral network that will allow for cross-country referral among the 55 member countries. The initiative is anchored within the Africa CDC [Regional Integrated Surveillance and Laboratory Network \(RISLNET\)](#), lending credence for acceptance of the initiative. As such, Africa PGI will further support regional use-case priority settings, as well as foster joint regional collaborations for outbreak response and endemic disease control and elimination.

Developing the laboratory workforce

The initiative will support the training of laboratory technicians, bioinformaticians and public health specialists. These professionals will then facilitate the generation, analyses and translation of pathogen genomic data for public health planning and policy decisions.

Creating enabling mechanisms to support sustainable genomics-based surveillance on the continent

The initiative will also facilitate the development of harmonised continental policies and guidelines to ensure best practices in biological specimen collection, storage and utilization; the referral of specimens to reference genomic centres and biorepositories; and the ethical use and archiving of genomic data. Additionally, the initiative aims to sustain genomics-based surveillance by employing price reduction mechanisms, such as collective bargaining and bulk procurement systems for genomic equipment and kits.

Implementing genomics for priority use-cases

Africa PGI will also support the implementation of regional and country priority genomics-use cases as identified by the countries and the community of experts. This will include implementing genomics to prevent and respond to emerging and re-emerging infections, monitor and control antimicrobial resistance and facilitate the control and elimination of endemic infectious diseases. An active community of experts will be engaged to support the sharing of best practices and affordable genomics tools, as well as the setting of standards and priority genomics-use cases in alignment with regional and country priorities.

Together, these activities will support the creation of a functional, continent-wide pathogen genomics surveillance system, a skilled workforce and tools to help Africa CDC and NPHIs fulfil their mandate of reducing the burden of infectious diseases and proactively counter emerging and re-emerging infections.

Progress

Taking note of the urgency to monitor SARS-COV-2 variants of concern on the continent, Africa CDC has been working jointly with partners to support the establishment of genomic surveillance systems in all countries. From these systems, representative samples are routinely sent to the Africa CDC-World Health Organization SARS-CoV-2 genomic surveillance network (**Figure 1**). Under Africa PGI, countries will be supported on sample shipment, data curation and analysis, as well as interpretation.

By 23 February 2020, variants of concern have been reported in 18 African countries. The 501Y.V2 variant had been reported in ten countries, including Botswana, Comoros, Democratic Republic of Congo, Ghana, Kenya, Malawi, Mozambique, South Africa, The Gambia, and Zambia. The 501Y.V1 variant has been reported in eight countries, including the Democratic Republic of Congo, Gabon, Ghana, Morocco, Nigeria, Senegal, South Africa and The Gambia.¹⁸

Conclusion

Overall, the devastating impact of the current COVID-19 pandemic is another resounding wake-up call to urgently strengthen preparedness and response systems against potential health threats on the continent. Africa PGI's integration of genomic technologies within more than 20 NPHIs and support for continental and regional networks are major steps towards democratising pathogen genomics to accelerate uptake and attainment of the African Union's [Africa Health Strategy 2016-2030](#) and [Agenda 2063](#) – an Africa devoid of disease threats.

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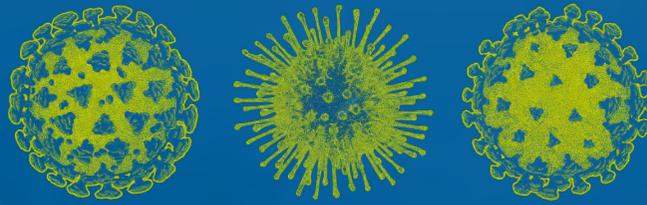
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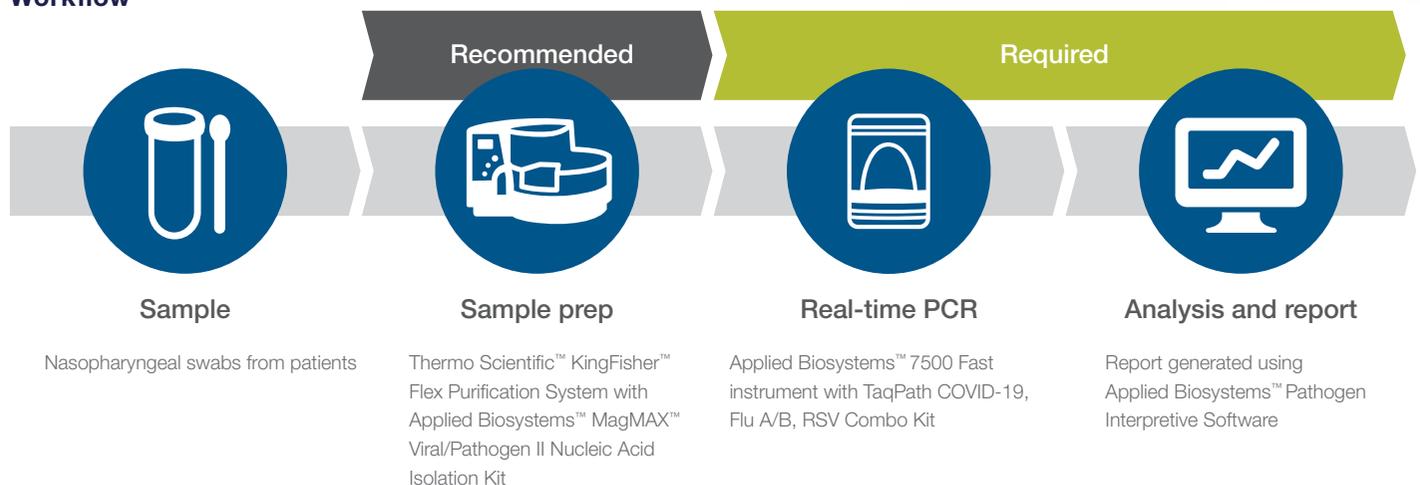
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Impact of SARS-CoV-2 variants on current diagnostic testing practices

Background

Diagnostics play an essential role in our response to the coronavirus disease 2019 (COVID-19) pandemic, helping to reduce disease spread through the identification of infected individuals, and providing epidemiological data to inform public health interventions by governments. The recent emergence of several new variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, has raised concerns due to the potential for increased transmissibility, increased clinical severity, and escape from vaccination or treatment efficacy. Furthermore, current diagnostic tests may not detect these new variants, potentially impeding the effectiveness of overall pandemic management strategies.

New variants of SARS-CoV-2 arise through mutations in the viral genome. Primers included in reverse transcription real-time polymerase chain reaction (RT-PCR) tests, the standard method for diagnosis, target specific sequences in the SARS-CoV-2 genome; therefore, if a mutation occurs in the targeted viral sequences, the primers could fail to detect the virus leading to inaccurate results. Additionally, genetic mutations leading to a structural change in the viral proteins targeted by antigen tests or antibodies targeted by serological tests could negatively impact the diagnostic performance of these assays. Fortunately, analysis of the specific mutations carried by the novel variants suggests that most tests currently used in primary detection of SARS-CoV-2 are not affected. Nevertheless, testing programmes and laboratories must be aware of the potential negative effects on certain diagnostic tests, to be able to rapidly take the necessary precautionary measures.

Three new variants of concern

Three SARS-CoV-2 variants have been designated 'variants of concern'

(VOC). These are B.1.1.7 (also known as VOC-202012/01 or 501Y.V1),¹ B.1.351 (or 501Y.V2),² and P.1 (or 501Y.V3).³ B.1.351 was first identified in South Africa and has spread across the continent, with cases detected in Mozambique, Mayotte, Zambia and Botswana (**Figure 1**).^{4, 5} B.1.1.7 was first identified in the United Kingdom, and has spread around the globe; several cases have been reported in Nigeria and Ghana (**Figure 1**).^{4, 5} P.1. was first identified in Brazil and has spread to Europe, Asia, the United States and in Latin America.^{4, 5} P.1. has not yet been identified in Africa as of 1 March 2021.

All three VOCs have several mutations in the S gene that encodes the spike protein – glycoprotein found on the surface of the virus. Much attention has been focused on the N501Y, E484K and K417T S gene mutations, because they lie in the receptor-binding domain of the spike protein, giving the viruses the potential to avoid antibodies and treatments based on the original sequence. Additionally, the VOCs also have several other mutations elsewhere in the S gene, and in other genes (**Figure 2**).

New variant under investigation

Recently, the emergence of a new variant of SARS-CoV-2, known as B.1.525, has been reported across the globe. As of 1 March 2021, sequences with the characteristic mutations of this lineage have been reported in 19 countries across Europe, North America, Oceania, Asia and Africa, although to date, Nigeria is the only African country to have reported >10 cases. The first detected B.1.525 case in Nigeria was from a sample collected on 23 November 2020 from a patient in Lagos State. The new B.1.525 variant has S gene mutations E484K, Q677H and F888L, and shares similar deletions with B.1.1.7. Although B.1.525 is not yet considered a VOC, it may



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have higher transmissibility with an increased risk of disease severity and vaccine escape, because it shares mutations with B.1.1.7, B.1.351 and P.1.

Anticipated impact of variants on diagnostic test performance

Fortunately, it is well known that mutations can arise, so molecular tests can target more than one gene. Thus, in the case of mutations in the SARS-CoV-2 S gene, the detection of novel variants is preserved due to the targeting of multiple genes. For example, a deletion at position 69/70 in the spike protein results in 'S-gene dropout'; whereby, the S-gene part of one commercially-available test is negative for B.1.1.7 samples.⁶ However, as the test also targets two other genes, and remains positive for these, it can still detect the virus. Notably, variant B.1.525 carries the same deletion at position 69/70 and so, the test is still expected to return positive results for this variant.

To date, there have been no reports of molecular tests being affected by other mutations carried by the new variants. However, given the number

of mutations in the S gene that each variant carries, laboratories that use molecular tests with primers targeting the S gene are recommended to monitor for 'dropout' and consider implementing assays specific for other genomic targets, if this is not already included as part of the existing test menu (**Table 1**).

Most antigen tests for SARS-CoV-2, including lateral flow rapid

diagnostic tests (RDTs), target the nucleocapsid protein, encoded by the N gene. Although B.1.1.7 and B.1.351 contain mutations in the N gene, they are found at the N-terminus of the protein; whereas, the majority of nucleocapsid-based

Countries with ≥10 reported cases

- B.1.1.7
- B.1.351

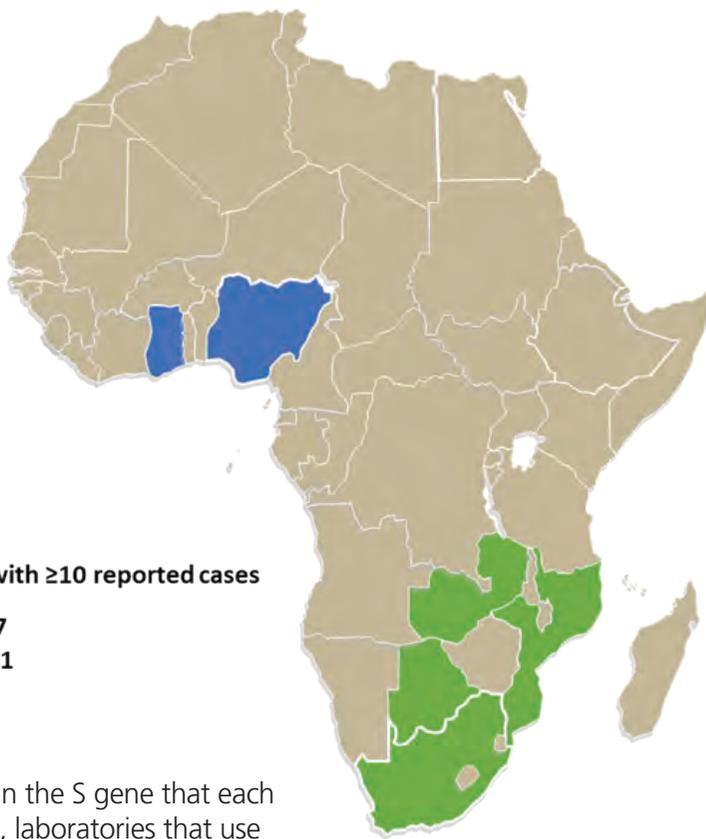
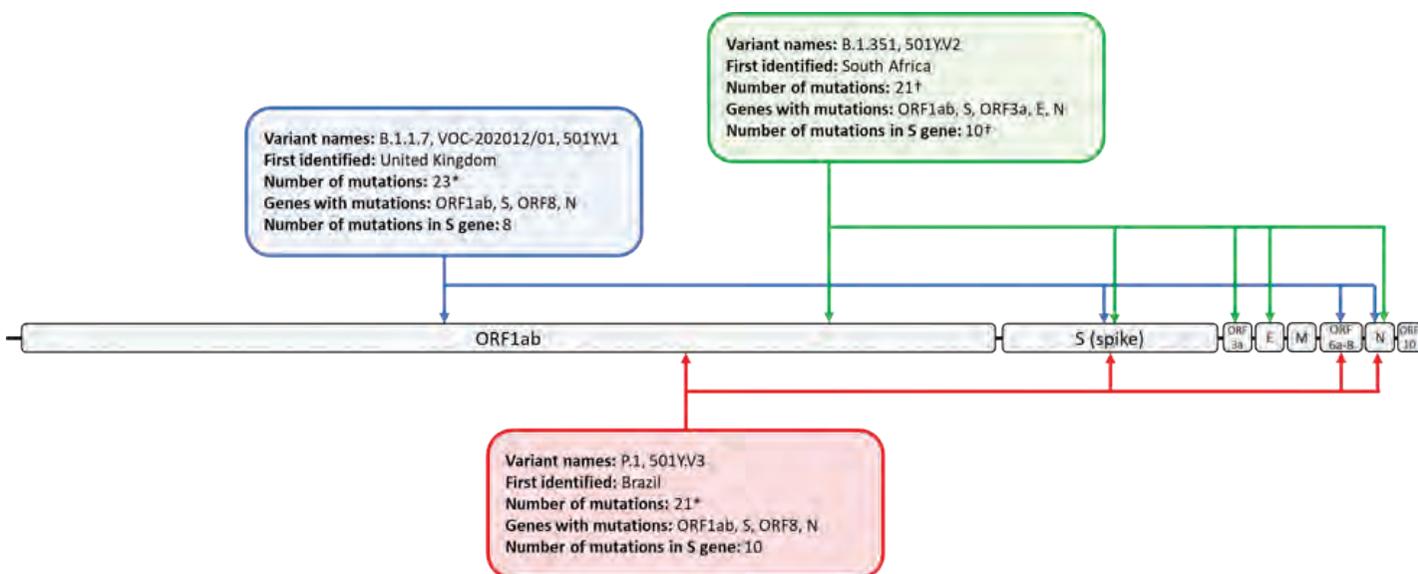


Figure 1. African countries with ≥10 reported cases of B.1.1.7 or B.1.351 (as of 1 March 2021) (4, 5)



*Includes 6 synonymous mutations for B.1.1.7 and 4 for P.1. Synonymous mutations are changes in the nucleotide sequence that do not change the amino acid sequence of the resulting protein.
 †Includes one mutation and one deletion at the same site

Figure 2. Location of mutations in the SARS-CoV-2 genome of three VOCs (based on data from Rambaut et al. (1), Tegally et al. (2) and Faria et al. (3))

Test design	SARS-CoV-2 variant			
	B.1.1.7 (VOC-202012/01 or 501Y.V1)	B.1.351 (501Y.V2)	P.1 (501Y.V3)	B.1.525
Molecular diagnostics (e.g. PCR tests)	Minimal impact 69/70 deletion can cause S gene dropout	Minimal impact No data on the impact of mutations on assay performance but may impact assays that target S gene sequences		Minimal impact 69/70 deletion can cause S gene dropout
Antigen detection tests (including rapid lateral flow devices)	<p>Most antigen detection tests target the C-terminus of the viral nucleocapsid protein, encoded by the N gene; a few target the spike protein</p> <p>Minimal impact The N gene mutations in these VOCs are located at the N-terminal. An assessment by Public Health England found that six SARS-CoV-2 rapid antigen tests targeting the nucleocapsid protein all successfully detected the VOCs</p>		<p>Minimal impact anticipated To date, evaluation studies have not been carried out to confirm that test performance is not affected, but no major performance deficits are anticipated for tests targeting the nucleocapsid protein</p>	
Serological antibody tests	No data	No data	No data	No data
	Potentially, the performance of assays detecting antibodies to viral spike protein or nucleocapsid may be affected, but to date, no evaluations have been performed			

Table 1. Anticipated impact of new SARS-CoV-2 variants on performance of different types of diagnostic tests (adapted from <https://www.finddx.org/7>)

antigen RDTs target the C-terminus. Antigen test performance is therefore not expected to be impacted by these VOCs. Accordingly, a study by Public Health England evaluated the performance of six SARS-CoV-2 rapid antigen tests (Abbott Panbio, Fortress, Innova, Roche/SD Biosensor nasal swab, Surescreen and Orient Gene), and found that all six tests were able to successfully detect the B.1.1.7 and B.1.351 VOCs.⁸ P.1 and B.1.525 also have N gene mutations at the N-terminus. Although there are no data on antigen test performance against these variants to date, based on experience with B.1.1.7 and B.1.351, no major performance deficits are anticipated for nucleocapsid-targeted tests. The performance of antigen tests that target the spike protein, however, could be impacted by any of the mutations in the VOCs or B.1.525.

The performance of all antibody tests may be potentially impacted by the new variants. Because these assays do not directly detect the virus, but rather the immune response generated in response to infection, it will take longer to understand how the performance of individual assays may be impacted by each variant. It is anticipated that tests that detect antibodies specific to the spike protein may be more impacted than those that are specific for the nucleocapsid protein, given the number of mutations in the S gene of the new variants. However, as antibody tests are generally not used for primary diagnosis, the overall impact of this on testing programmes is likely to be insignificant.

Impact on current testing practices: experience from Nigeria

The B.1.1.7 VOC and the B.1.525 variant have been identified in Nigeria. All the samples with these variant strains were collected from patients between November 2020 and January 2021. To further study

the impact of variants on diagnostics, transmission, disease severity and new vaccines implementation, the Nigeria Centre for Disease Control (NCDC), in collaboration with other Nigerian institutions with SARS-CoV-2 sequencing capacity, has launched a genomic surveillance network tasked with continuous monitoring of circulating SARS-CoV-2 variants using next generation sequencing platforms.

To date, all molecular RT-PCR kits used nationally target at least one SARS-CoV-2 gene in addition to the S gene. This ensures that the mutations in the S gene described in **Figure 2** do not hinder the detection of the virus.

Regarding point-of-care testing platforms, two World Health Organization-approved antigen RDTs are in use in Nigeria: Abbott Panbio and Roche/SD Biosensor, along with Medica/LumiraDX, a device-based antigen-detection test. Fortunately, recent studies have demonstrated that the two RDTs are not likely to be impacted by B.1.1.7 and B.1.351 VOCs.

Finally, to ensure that high-quality diagnosis of COVID-19 is maintained, the NCDC National Reference Laboratory has implemented measures to monitor SARS-CoV-2 diagnostic activities through an External Quality Assurance (EQA) programme. As part of the EQA programme, SARS-CoV-2 panels are systematically distributed to COVID-19 testing laboratories to assess proficiency in performing molecular detection of SARS-CoV-2. A recent EQA panel produced at the NCDC National Reference Laboratory included sequences of all positive SARS-CoV-2 samples collected between the months of January and February 2021. Most samples were either B.1.1.7 or B.1.525. Both variants tested positive on all diagnostic assays including antigen RDTs and molecular PCR tests.

Future perspectives

As the pandemic continues, new variants of SARS-CoV-2 will continue to emerge. The rapid emergence of novel variants demonstrates not only the need for robust and widespread genomic surveillance to ensure prompt detection of mutations, but also for continued monitoring of diagnostic test results to identify changes in test performance that will inform amendments to the testing panel.

Note: Some information contained in this article is taken from rapidly published articles that have not been peer-reviewed.

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Guidance for HPV screening initiatives in Africa:

How assay design and performance can improve test participation

Cervical cancer burden in Africa

Globally, upwards of 600 000 women are diagnosed with cervical cancer each year, resulting in more than 340 000 estimated deaths annually.¹ A staggering 19 out of the 20 countries with the greatest cervical cancer burden are in Africa,² making it the continent's second most prevalent cancer. These figures reflect the disparity between countries (**Figure 1**),^{3,4} largely based on income and access to resources, age of the population, and the incidence of HIV among other factors. Africa has a young population. Because cervical cancer tends to affect women in this demographic, the disease has a significant social impact on African communities. The major risk factor for cervical cancer is, of course, persistent human papillomavirus (HPV) infection, and the prevalence of this cancer increases with HIV positivity; women living with HIV are six times more likely to develop cervical cancer, compared to HIV-negative women,⁵ largely due to their lowered immune response. Crucially, cervical cancer can be entirely preventable with proficient testing, vaccination and management, but so far, a lack of resources, funding and awareness has engendered only limited and predominantly opportunistic cervical cancer screening in many countries and a limited introduction of HPV testing into clinical settings.

In November 2020, the World Health Organization (WHO) announced its Global Strategy to Accelerate the Elimination of Cervical Cancer⁶ to address this situation, shining a spotlight on the need for access to HPV testing in Africa, particularly in low- and middle-income areas, and securing funding for

screening programs. Rates of cervical cancer incidence and deaths continue to rise rapidly across Africa, and the WHO warns that, without effective intervention, this will continue to escalate. Comprehensive vaccination programs and HPV screening and treatment are now planned and aim to reduce the incidence of cervical cancer and alleviate the disease burden in Africa.

HPV testing and the WHO initiative

Testing for cervical HPV helps to screen for patients who may go on to develop cervical cancer, allowing a far earlier diagnosis and effective disease management. The WHO elimination strategy targets for HPV are 90-70-90, meaning 90% vaccine coverage, 70% of women screened before the age of 35, and 90% treated, with the ultimate aim being to reduce the global incidence of cervical cancer by 10% by 2030.⁴ Therefore, efficient strategies are needed for implementing effective screening programs in public and private healthcare settings.

HPV testing involves the screening of cervical cells using a PCR-based molecular diagnostic assay that detects the presence of high-risk types of HPV and is both validated and endorsed internationally as a replacement to cytology-based screening (i.e., 'Pap smears'). The HPV tests are designed to detect oncogenic HPV genotypes and, therefore, provide a binary answer with respect to cervical cancer risk. In women who test positive for oncogenic HPV, there is the potential for HPV progression along the dysplasia sequence in the cervix to invasive cancer; whereas, those who test negative for oncogenic HPV have a minimal risk of developing a high



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Estimated age-standardized incidence rates (World) in 2020, cervix uteri, all ages

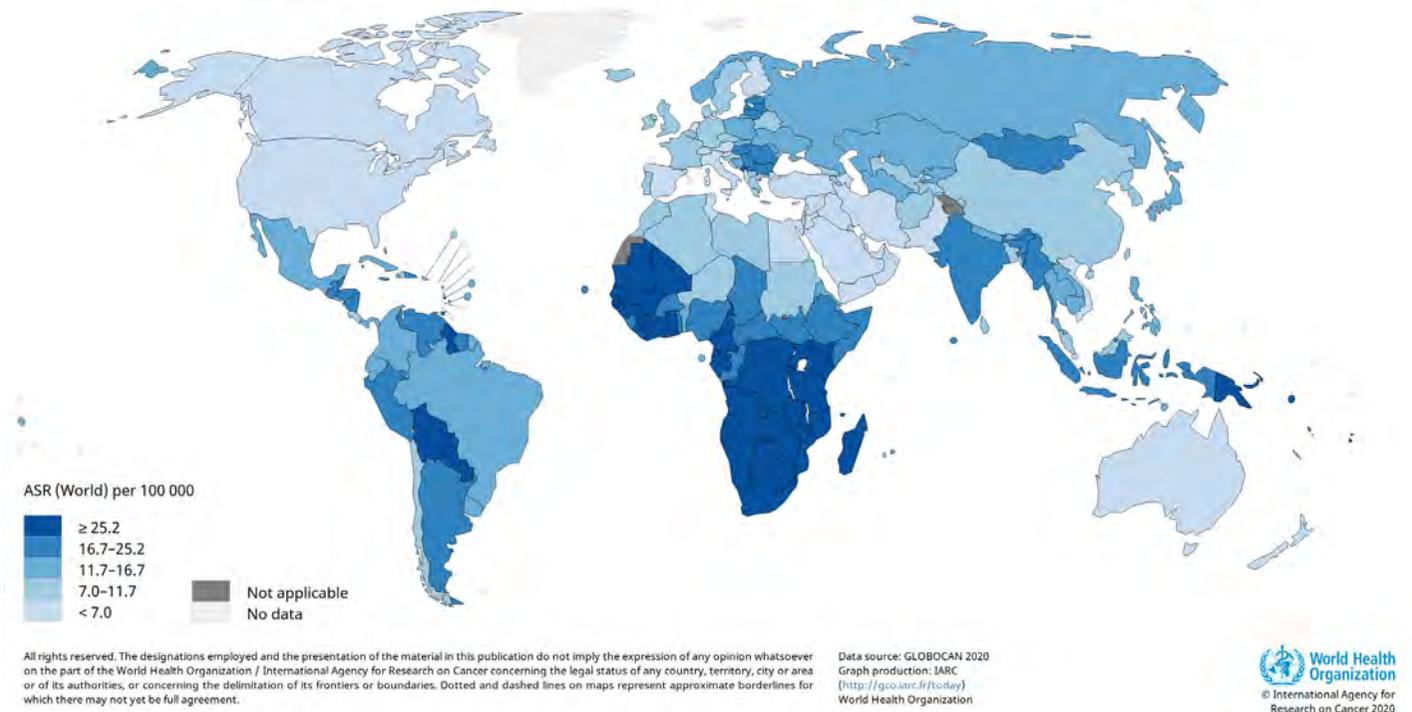


Figure 1. Global incidence rate of cervical cancer based on age, World Health Organization

grade squamous intraepithelial lesion. However, for risk stratification purposes, current assays provide far more sophisticated information than this, particularly about specific genotypes. The majority of HPV strains are transient, and most sexually active women and men will be infected at some point in their lives. In fact, 95% of invasive cervical cancer cases are caused by just 14 HPV strains and, of those, HPV 16 and HPV 18 are the highest risk and together account for 70% of invasive cancers.⁷ Clinicians can stratify patients by determining both the presence and genotype of HPV, and streamline them for further investigations and treatment. In a setting with limited resources, this risk stratification based on genotype to prioritise the highest risk patients is essential for relieving the burden on colposcopy or ablation services. Women with HPV 16 and HPV 18 have a higher incidence of high-grade dysplasia and higher incidence of progression; as such, management algorithms

prioritise this subset of women for immediate treatment. The subset of patients with non-16, non-18 oncogenic HPV genotypes have a lower risk of high-grade lesions and a lower risk of progression and are therefore best further evaluated with an additional triage test, most commonly cytology analysis, to determine the stage of progression of the woman down the continuum of dysplasia, and to stratify for referral and therapy or follow up. The extremely high negative predictive value of HPV-based testing allows for safely extending the interval between screening events in oncogenic HPV-negative women. In high resource settings, the recommended screening interval is 5 years for HPV-negative women. In lower resource settings, the interval that is likely to be achievable is a 10-year screening interval.

Historically, cervical cancer screening has been performed by examining cervical cells under a microscope with morpho-

logical evaluation, and recently this evolved to using liquid-based collection methods. The cytology sample is taken directly from the cervix and requires a skilled health-care worker in a clean setting with access to resources, such as a speculum, good lighting and a medium to preserve the sample. However, this labour-intensive and human resource-dependent procedure has a low throughput at a high cost, hindering the scalability of screening. In contrast, HPV testing involves the detection of stable viral DNA in cervical cells; thus, there is the potential to simplify sampling and detect HPV DNA in cells that have been shed from the cervix into the vaginal canal. In addition to the benefits of sensitivity and risk stratification with genotyping described above, there is even the possibility for using self-sampling techniques, if a method can be established that would give enough sensitivity, and this would drastically increase the scale of testing and likely encourage more participation.⁸ The cost

of the HPV test has also now come down to a more affordable screening price, and the technology, for the most part, is the same as HIV viral load testing, allowing access to pre-existing infrastructure across Africa.

Introducing HPV testing to clinics and laboratories

So, assuming we now have a sensitive, efficient test for cervical cancer risk, how do we roll out a screening program? At this point, it is important to balance age-dependent screening intervals with access to resources and medical capacities. Guidance is usually given in a tiered system based on resources (Table 1) and highlights how many times a woman should be screened in her lifetime and over what age ranges.⁹ The progression to invasive cervical cancer from persistent HPV infection is time-dependent, so it is not appropriate to screen women at a young age when most HPV infections spontaneously clear, and the disease burden in terms of high grade cervical intraepithelial neoplasia and invasive carcinoma is very low. In high resource settings, screening should start at 25 years, and occur every five years, until the patient is

aged 65-70 years, provided that no high-risk HPV genotypes are detected. However, where resources are more limited, longer intervals between tests can be implemented with the goal of screening every woman three times in her lifetime, starting at the age of 30. It is only with the high sensitivity and high negative predictive value of HPV-based screening that one can safely increase intervals across a population. The American Society of Clinical Oncology recommends that even in low resource settings, if a woman receives just one single cervical screening test in her lifetime, this should be an HPV-based screening test (Table 1).⁹ Those who test positive for high-risk HPV should be managed according to guidelines for the particular health system. In general, this management would include immediate referral of HPV 16- and HPV 18-positive women for colposcopy and ablation where available, or ablation where colposcopy is not available, and triage with cytology or follow up of non-16, non-18 HPV-positive women. With a combination of screening intervals and cytology, we can create a staging process for patients and fast track the management of patients most at risk.

HPV screening tests and the associated laboratory hardware have evolved rapidly over the past decade. The spectrum of tests now available includes assays that can be safely and effectively deployed in different resource settings. In addition, the African continent has seen a broad development and implementation of molecular diagnostic services to serve the needs of the HIV management program and is therefore uniquely prepared for the implementation of an HPV-based cervical screening program.

The following factors, in no particular order of importance, are key considerations in selecting HPV-based screening assays for implementation in the individual health systems on the African continent:

- The cervical cancer screening program should ideally integrate with existing programs, such as HIV viral load, with respect to shared hardware and laboratory capacity.
- The supporting hardware for an assay should allow for appropriate scaling of the program and throughput.
- The assay should, at a minimum, include partial genotyping for

Resource Strata	Method of Screening	No. of Screens in a Lifetime	Age Range (years)	Management of HPV-Positive Patients
Maximal	HPV	9	25-64; every 5 years	Triage to colposcopy by HPV genotyping* and/or cervical cytology (Pap)
Enhanced	HPV	5	30-64; 30, 34, 44, 54, and 64	Triage to colposcopy by HPV genotyping* and/or cervical cytology (Pap)
Limited	HPV	2-3 times	30-49	Triage to treatment by HPV genotyping,* VIA, and/or cervical cytology (Pap); VAT†
Basic	HPV‡	1-3 times	30-49	VAT†

Abbreviations: HPV, human papillomavirus; Pap, Papanicolaou; VAT, visual assessment for treatment; VIA, visual inspection with acetic acid.

NOTE. Adapted from www.asco.org/rs-cervical-cancer-secondary-prev-guideline.

*HPV16 and HPV18 or HPV16, HPV18, and HPV45.

†Determine what kind of treatment is appropriate.

‡Can start with VIA until HPV testing becomes available, permitting the development of health service delivery infrastructure.

Table 1. Resource-stratified guidelines for screening women for high-risk HPV, American Society of Clinical Oncology © 2017 by American Society of Clinical Oncology

HPV 16 and HPV 18 to identify the most at-risk women and streamline subsequent management.

- HPV-based screening assays should include an internal cellular genomic control to ensure that sampling is adequate; this is particularly important looking forward to the potential of self-sampling in women.
- The assay should ideally be adaptable to include self-sampling with a validated device in future.
- The assay should have a high negative predictive value, sensitivity and specificity for oncogenic HPV detection supported by sufficient analytical and clinical validation data.
- The HPV-based screening program should ideally be coupled with a cytology service, where available, to effectively triage HPV-positive women for subsequent management.

Conclusion

The WHO's Global Strategy to Accelerate the Elimination of Cervical Cancer has highlighted the need for efficient vaccine, screening and treatment programs across Africa. HPV screening at regular intervals throughout a woman's life is the most effective and reliable method for the detection of cervical cancer risk. The long interval between initial exposure to high-risk HPV and the development of high-grade dysplasia provides a unique window to identify women at risk and effectively manage them to prevent the development of invasive cancer. Choosing the right assay with appropriate workflow, design and performance criteria is essential in order to integrate HPV tests quickly and easily into African clinics and laboratories. Successful implementation of programs based on the right assay can help to reduce the

incidence of cervical cancer and the disease burden across Africa.

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Scaling up laboratory testing for COVID-19 in Cameroon

Challenges, lessons learnt and perspectives

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, molecular testing (PCR) has been a critical component of the public health response, being the most sensitive and reliable test for detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, molecular testing requires equipment, laboratory infrastructure and skilled human resources lacking in most low- and middle-income countries (LMICs).¹ As the COVID-19 pandemic unfolded, these countries had to gradually improve their molecular testing capacities.

SARS-CoV-2 Testing in Cameroon

Cameroon, an LMIC, began performing molecular testing to detect SARS-CoV-2 on 1 February 2020. The first COVID-19 case was detected by the 'Centre Pasteur du Cameroun' (CPC), the National Reference Laboratory for respiratory infections, on 5 March 2020, making Cameroon the twentieth African country affected by COVID-19. Molecular testing for COVID-19 at CPC was possible thanks to initial support from the Institut Pasteur International Network and influenza surveillance programmes. Being the only COVID-19 molecular testing laboratory in Cameroon at the time, all suspected cases were referred to CPC for testing. As the number of COVID-19 positive cases surged in major cities, despite mitigating measures, such as border closure and restricted gathering,⁴ the demand for testing rapidly ballooned. From testing 10 samples per day on 6 March 2020, CPC had to subsequently test hundreds of samples from all over the country and to deliver results within 24 hours to facilitate patient isolation and contact tracing. Working non-stop to diagnose the growing number of suspected COVID-19 cases was not

sufficient to cover the demand, and transporting samples from distant regions delayed diagnosis.

Therefore, molecular testing had to be decentralized to cope with the skyrocketing demand. As such, decentralizing molecular testing in Cameroon was not a question of 'why' but of 'how'. To address the 'how' question, on 27 March 2020 the Minister of Public Health tasked CPC to set up and implement a decentralized plan for COVID-19 molecular testing in collaboration with the National Public Health Laboratory and the Centre for Research and Military Health.³ To fulfil this goal, a four-step process was set up.

The first step was to identify and evaluate laboratories across the country with open platforms that could run several RealTime-PCR (RT-PCR) protocols from different manufacturers. Therefore, a questionnaire was sent out to all clinical, public health and research laboratories in the 10 regions of Cameroon, to collect information on available extraction and amplification equipment, existence of safety cabinets and infrastructure to handle biological specimens as required by the World Health Organization (WHO),² and staffing.

The second step was to select laboratories that could immediately start testing using the available COVID-19 diagnostic kits from the identified laboratories with open RT-PCR platforms. These kits were provided through a donation by the Alibaba Foundation. Biocentric extraction kits were made available by the Global Fund through the HIV Program. Unfortunately, these extraction kits were usable only in laboratories equipped with the required semi-automated instrument. By 10 April, Cameroon had moved from one to four laboratories performing COVID-19 molecular testing, with the laboratories located in three out of the 10 regions in



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Members of the Cameroon COVID-19 testing laboratories, December 2020 (Source: Sylvanus Akoaghe)

Cameroon: North, Central and Littoral. In April 2020, the Global Fund once again provided support with a new consignment of extraction kits that could be used by most laboratories. Hence, by the end of the same month, four other laboratories were added to the network, extending laboratory testing to two new regions: Northwest and East, and placing two additional laboratories in the Central region. With a strong commitment from the government and support from partners, more

diagnostic kits became available, and two other laboratories, one in the Central region and one in the Southwest region were added to the network. By the end of May 2020, Cameroon could rely on 10 COVID-19 diagnostic laboratories in six regions. However, the number of laboratories still fell short of the target: provision of a COVID-19 diagnostic laboratory in every region of the country to provide rapid COVID-19 testing and reduce delays.

Positive news came when the diagnostics companies Abbott and Cepheid launched new tests for COVID-19 on their platforms (Abbott m2000sp and GeneXpert automated systems, respectively). These platforms were already being used for HIV and tuberculosis diagnosis in Cameroon. The third step then was to evaluate and redirect these platforms for COVID-19 testing. Procurement of the new Abbott RealTime SARS-CoV-2 and Cepheid Xpert Xpress SARS-CoV-2

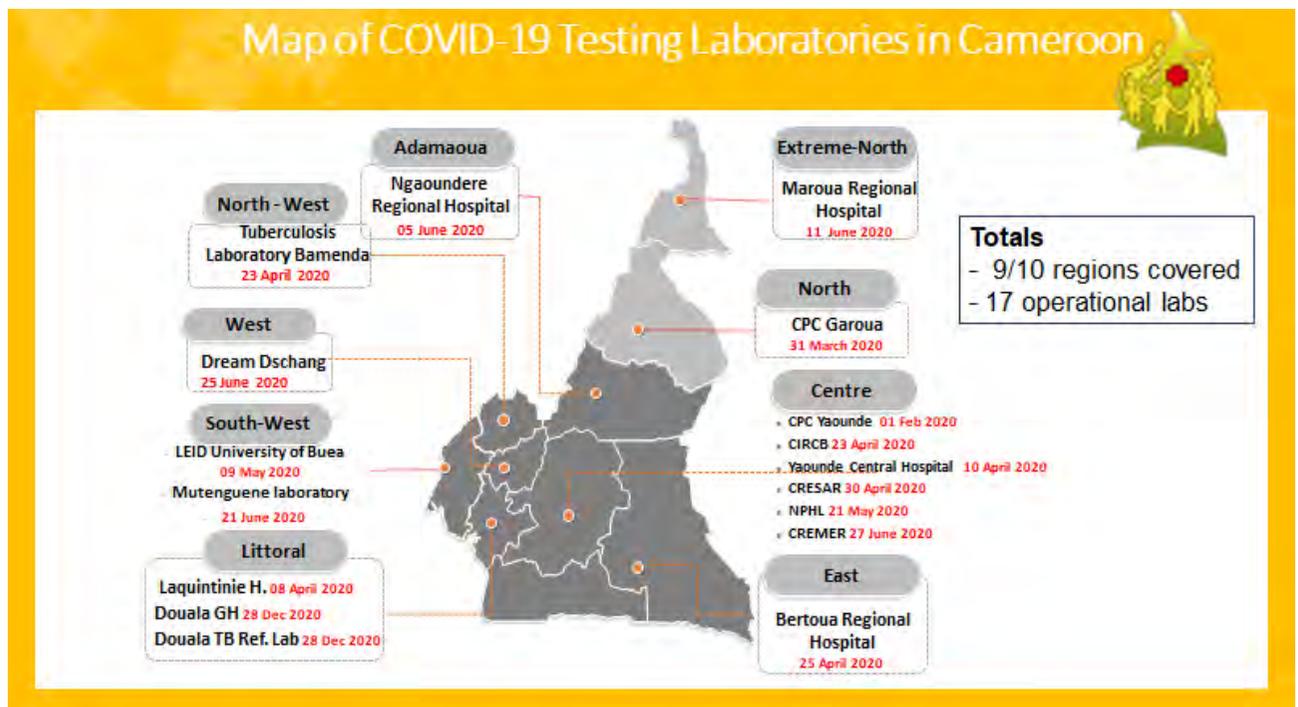


Figure 1. Map of COVID-19 testing laboratories in Cameroon as of December 2020

diagnostic kits was possible through the WHO-coordinated COVID-19 supply portal, which determines the quantities of COVID-19 test kits to be supplied to each country. Through this portal, 3000 Xpress SARS-CoV-2 diagnostic kits were supplied to Cameroon. Given the low number of kits received, priority was given to two additional regions where testing laboratories only had the GeneXpert diagnostic platform. Thus, in June 2020, two laboratories in the Adamawa and Far North regions were able to perform COVID-19 molecular diagnosis, enlarging the network to 12 laboratories. A similar approach was adopted once the Abbott RealTime SARS-CoV-2 diagnostic kits

were included into the network. By December 2020, Cameroon had 17 operational COVID-19 molecular testing laboratories in nine of the 10 regions of the country (**Figure 1 and Table 1**).

The last step of the decentralization process focused on two key aspects: establishing a reagent and consumable supply chain to supplement the laboratories and establishing a sample referral and reporting system. To successfully monitor COVID-19 testing in real time across the different laboratories, a data collection and reporting platform already developed and used by CPC called the 'Platform for Collecting, Analysing and Reporting Data' (PlaCARD),⁵ was adapted to report-

from ensuring biosafety measures to coping with limited supply of laboratory reagents and consumables. Even when supplies were available, quantities could only sustain testing for a couple of weeks, requiring the identification of new supply chains and frequent ordering, deployment, and transportation of available test materials to laboratories. Standardized testing procedures had to be constantly and quickly adapted to market-available supplies. Furthermore, additional staffing was necessary to sustain COVID-19 testing in the different regions. With the financial support of the WHO, the Foreign, Commonwealth and Development Office, and the Ministry of Public Health-Agence Française de Développement-Kreditanstalt für Wiederaufbau programs, a total of 54 staff members, including experts, technicians, and data entry clerks, were trained in COVID-19 testing, reporting and biosafety by CPC and deployed in the different laboratories. Redirecting diagnostic capacity typically used for HIV and tuberculosis diagnosis towards COVID-19 testing may have affected these services.¹ However, the laboratories adapted their schedule to accommodate COVID-19 testing within their testing programme by extending their operational hours overnight.

COVID-19 has pushed Cameroon's health system to its limit, revealing long-standing existing gaps in laboratory testing systems. Conversely, the nation's response has offered useful opportunities to foster improvement of its laboratory testing system. The decentralization process improved sample referral, real-time reporting, and integration of laboratory services. It is time to move towards more integrated laboratory services. Prioritizing key diseases, such as HIV, malaria and tuberculosis in LMICs, has resulted in under-utilized laboratory services aimed at diagnosing only a few diseases.¹ The COVID-19 pandemic has

Developing a data monitoring and management platform called "PlaCARD" to collect, analyze and report COVID-19 testing results.

Historically, the Centre Pasteur du Cameroon (CPC) has been a key participant in disease surveillance and response activities in Cameroon. As the National Reference and Public Health Laboratory, CPC monitors and tracks about 20 diseases (cholera, measles, rubella, yellow fever, polio, rabies, influenza, respiratory infections, bacterial meningitis, viral hemorrhagic fevers, chikungunya, dengue fever, tuberculosis, malaria, HIV, leprosy, Buruli ulcer, etc.) and regularly reports to the Ministry of Public Health. The Epidemiology and Public Health Service of CPC has developed and deployed a data collection and monitoring platform called 'PlaCARD', which stands for the Platform for Collecting, Analysing and Reporting Data, for disease surveillance.. The PlaCARD platform supports the District Health Information Software 2 platform with tools, such as data extraction in an intranet or internet network, data transfer, data compilation, analysis, visualization and report editing. PlaCARD can also interact with other databases and allows the use of mobile tools, such as smart phones and tablets, for data entry and collection.

were received, and three additional laboratories in the Southwest, West and Central regions were added to the network, increasing the number of laboratories to 15 across nine of the 10 regions of Cameroon. The decentralization strategy also sought to ensure that regions with high testing volumes had more than one diagnostic laboratory. As such, once a second consignment of 5000 Cepheid diagnostic kits and open platform RT-PCR equipment was available, two new laboratories in the Littoral region

ing of COVID-19 test results and implemented in all laboratories. The number of PCR tests performed and the number of positive cases could thus be assessed and reported on a daily basis.

Lessons learned

Overall, implementing and managing a decentralized molecular testing system unveiled challenges whose resolution helped to further strengthen the public health response. There were challenges at every phase of the testing cascade,

Region	Laboratory	Diagnostic assays/equipment available	Date testing began	No. of tests performed (as of Feb 2021)
Adamaoua	Ngaoundere Regional hospital	Xpert® Xpress SARS-CoV-2 test	05 June 2020	2465
Centre	Centre Pasteur du Cameroun (CPC)	Abbott Real Time SARS-CoV-2 assay, Open platform RT-PCR, Xpert® Xpress SARS-CoV-2 test	01 February 2020	55 026
	Centre for Research and Military Health (CRESAR)	Abbott Real Time SARS-CoV-2 assay, Open platform RT-PCR	30 April 2020	1932
	Chantal Biya International Research Centre (CIRCB)	Abbott Real Time SARS-CoV-2 assay, Open platform RT-PCR	23 April 2020	21 161
	Yaounde Central Hospital (HCY)	Open platform RT-PCR	10 April 2020	13 266
	Center for Research for Emerging and Re-Emerging Diseases (CREMER)	Abbott Real Time SARS-CoV-2 assay , Open platform RT-PCR,	27 June 2020	3562
	National Public Health Laboratory (NPHL)	Abbott Real Time SARS-CoV-2 assay, open platform RT-PCR	21 May 2020	20 817
East	Bertoua Regional Hospital	Open platform RT-PCR	25 April 2020	3893
Extreme North	Maroua Regional Hospital	Xpert® Xpress SARS-CoV-2 test	11 June 2020	1152
Littoral	Laquintinie Hospital Douala	Abbott Real Time SARS-CoV-2 assay, open platform RT-PCR, Xpert® Xpress SARS-CoV-2 test	08 April 2020	60 018
	Tuberculosis Reference Laboratory Douala	Xpert® Xpress SARS-CoV-2 test	28 December 2020	1808
	Douala General Hospital	Open platform RT-PCR	28 December 2020	4932
North	Centre Pasteur du Cameroun, Garoua subsidiary (CPC AG)	Open platform RT-PCR, Abbott Real Time SARS-CoV-2 assay, Xpert® Xpress SARS-CoV-2 test	31 March 2020	2542
North-west	Tuberculosis Reference Laboratory Bamenda	Abbott Real Time SARS-CoV-2 assay, Open platform RT-PCR, Xpert® Xpress SARS-CoV-2 test	23 April 2020	6475
Southwest	Laboratory for Emerging Infectious Diseases, University of Buea	Open platform RT-PCR	09 May 2020	5335
	Reference Laboratory for HIV Early Infant Diagnosis, Mutengene	Abbott Real Time SARS-CoV-2 assay	21 June 2020	1753
West	DREAM Laboratory Dschang	Abbott Real Time SARS-CoV-2 assay	25 June 2020	4856

Table 1. Available diagnostic platforms and number of tests performed by each COVID-19 testing laboratory, Cameroon

taught us that single disease testing platforms can be transformed into multi-disease testing platforms. If properly managed, such platforms could significantly increase testing capacities and reduce costs. Setting up a COVID-19 diagnostic laboratory in the South region has been unsuccessful, and although the South region has a molecular device, it is the Abbott m-PIMA analyser, which only measures HIV viral load, emphasizing the need for setting up multi-disease testing platforms. The use of shared database systems, such as PlaCARD, will help enhance public health surveillance of diseases and improve the timeliness of results.

Overall, decentralized laboratory testing for SARS-COV-2 has been key to the control of COVID-19 in Cameroon. It has also paved the way for a more effective system of

infectious disease diagnosis and surveillance in the country.

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Meet Nancy Bowen

Nancy Bowen has been the Head of Kenya's National HIV Reference Laboratory (NHRL) within the Division of National Public Health Laboratory and Department of Laboratory Sciences since 2013. She holds a Master of Science Degree with a specialty in Infectious Disease Diagnosis (Virology), with more than 25 years of experience across various positions, ranging from a Medical Laboratory Officer and Laboratory Programme Officer to her current position. Her current roles and responsibilities involve overseeing all HIV serology, VL, early infant diagnosis (EID) and other HIV-related testing nationally, as well as coordinating proficiency testing under her docket of quality management systems. She is responsible for budget preparation and monitoring the implementation of the Cooperative Agreement between Kenya's Ministry of Health and the United States Centers for Disease Control, and she participates in the country's Global Fund activities. Leading various active HIV laboratory technical working groups and national surveillance activities in Kenya, she is the focal person for ASLM's Laboratory Community of Practice (LabCoP). In addition, Nancy coordinates and implements policies relating to COVID-19 molecular testing at the National HIV Reference Laboratory and at VL and EID laboratories in Kenya. She has also published her work in peer-reviewed publications and presented in various seminars both locally and globally.



Nancy Bowen, MSc
Head, National HIV Reference Laboratory, Division of National Public Health Laboratories, Kenya
(Source: Nancy Bowen)

under her docket of quality management systems. She is responsible for budget preparation and monitoring the implementation of the Cooperative Agreement between Kenya's Ministry of Health and the United States Centers for Disease Control, and she participates in the country's Global Fund activities. Leading various active HIV laboratory technical working groups and national surveillance activities in Kenya, she is the focal person for ASLM's Laboratory Community of Practice (LabCoP). In addition, Nancy coordinates and implements policies relating to COVID-19 molecular testing at the National HIV Reference Laboratory and at VL and EID laboratories in Kenya. She has also published her work in peer-reviewed publications and presented in various seminars both locally and globally.



NHRL staff with visiting Zambian team on south-to-south VL/EID country scale up bench marking outside the National HIV Reference Laboratory, KNH grounds, Nairobi, Kenya.

(Source: Nancy Bowen.)

What key experiences from your childhood, schooling or professional training led you to a career in laboratory medicine?

I am a medical laboratory scientist, and my areas of speciality are the diagnosis of infectious viral diseases and the management of HIV testing programmes. I am passionate about coordinating and implementing HIV laboratory policies, guidelines and strategies in the fight against HIV/AIDS.

I was attracted to medical sciences right from my primary school to the end of high school, due to my interaction with close relatives and friends working in the medical field. After high school, I, therefore, settled on Medical Laboratory Science, which opened doors to my current practice in laboratory medicine.



Nancy Bowen in Nairobi, Kenya
(Source: Nancy Bowen)

As the Head of the National HIV Reference Laboratory, what is your day-to-day role? How did you become the National Manager?

My day-to-day role involves providing technical guidance, oversight and coordination of HIV care and treatment services in the NHRL, which provides HIV testing services for both laboratory diagnosis and treatment monitoring. Diagnostic tests include EID, HIV serology and incidence testing, while treatment monitoring tests include VL, HIV drug resistance and CD4 count testing. I provide oversight to ensure my laboratory and all the other VL/EID testing labs in Kenya meet the second and third UNAIDS 95-95-95 global targets. Thus, in addition to managing the daily operations of NHRL staff, I also engage with key stakeholders and HIV technical working groups through scheduled meetings on implementing HIV policies. I also led the scale-up of VL/EID HIV testing laboratories from 4 laboratories in 2013 to 12 laboratories currently.

I am a medical laboratory scientist, and I rose through ranks with documented accomplishments. I

served as a Laboratory Manager in various government hospitals. I was a member of the Kenya Medical Laboratory Technician and Technologists board (KMLTTB) from 2000-2004. I have served as the program officer in charge of laboratory care and treatment at the Division of National AIDS and STI Control Programme (NAS COP), and later, I went on to serve as the deputy blood safety programme manager for more than 10 years. All these experiences and the managerial expertise I acquired contributed to my appointment as the Head of National HIV Laboratory.

What is the relationship of the National HIV Reference Laboratory and ASLM?

Our NHRL is under the Department of Laboratory Sciences within the Division of National Public Health Laboratory, and we play a key role in ASLM's LabCoP. LabCoP seeks to create a community of laboratories for sharing of best practises. The NHRL has played a significant

role in implementing ASLM LabCoP strategies in collaboration with other partners to increase access to HIV standards of care, CD4 testing and point-of-care diagnostics. ASLM, LabCoP and NHRL have collaborated in expanding VL capacity by providing a platform for sharing information, tools and resources to support policy implementation across the whole cascade of VL testing from demand creation to results utilization. The NHRL has participated in various ASLM-sponsored conferences, forums, trainings and meetings, including HIV laboratory-focused forums, such as one on VL external quality assessment programmes, to share knowledge and enhance staff capacity. The NHRL has also been a key example in these ALSM forums for good practices to be emulated by other country's reference laboratories. In addition, the NHRL and ASLM have been involved in responding to the COVID-19 pandemic through [ASLM's Coronavirus Action Center](#).



Representatives of the Kenyan team at the face-to-face LabCoP meeting in Kampala, Uganda, 15-17 October 2018.
(Source: Nancy Bowen)



Kenyan team group photo during the face-to-face LabCoP meeting in Kampala, Uganda, 15-17 October 2018. The Kenyan team received a certificate and award for the country making the most contributions in sharing best practices through the monthly ECHO sessions that year. (Source: Nancy Bowen)

What do you see as the most important emerging challenges related to scale up of VL testing in Africa over the next 5 years?

VL testing might be unsustainable, because of inadequate funding by host governments when donor funding decreases or a funding period is over. Also, equipment varies and changes with different protocols and results. This leads to varying and incomparable results, which can hinder future regional cross-country referral networks.

The lack of local production and consequent over-reliance on overseas importation of all VL and EID reagents and commodities is unsustainable. It leads to persistent stock outs due to customs, importation challenges and is financially costly. Lastly, the lack of biosafety and waste management systems to

ensure safe disposal of VL and EID waste containing guanidinium thiocyanate is a looming challenge.

How can ASLM work with your organization and others in your position



The Kenyan team at the face-to-face LabCoP in Addis Ababa, Ethiopia, 22-25 October 2019 with ASLM LabCoP team, Anafi Mataka and Dr Thandi. (Source: Nancy Bowen)



Nancy Bowen in her office at the National HIV Reference Laboratory in Nairobi, Kenya. (Source: Nancy Bowen)



Nancy Bowen at the University of Maryland, Boresha Mahabara (CDC laboratory partner) end-of-programme party, Nairobi, Kenya. (Source: Nancy Bowen.)

and molecular epidemiology. This is due to the dynamic nature of laboratory science with the emergence of new technologies that require different skill sets. Continuous training and mentorship within the continent will enhance the capacity of laboratory scientists and equip them to overcome challenges they might encounter. Also, they should seriously explore the wider need to engage in various public health programmes and work towards providing local solution to emerging health securities and challenges in the laboratory field.

to meet those challenges?

ASLM gives a voice to African scientists, and through its forums, such as LabCoP scientists from different African countries can gather to share best practices and discuss challenges. These brainstorming sessions give birth to recommendations and implementable actions that fill knowledge gaps and strengthen laboratory systems.

ASLM should work with the global manufactures to make a bold move towards local production of kits and reagents. This will reduce costs and allow local governments to be able to fund projects and own some of the proceeds. ASLM can work with our organization in coordinating with different part-

ners to highlight the significance of diagnostic scale up and laboratory system strengthening specific for a member state.

What is your best advice for the next generation of African laboratory scientists? How can they best equip themselves and their communities for the challenges to come?

The next generation of African scientists should pursue a medical profession in laboratory sciences. It is a very unique and novel field co-existing with medicine. A doctor cannot make any significant clinical decisions for patient management without a quality laboratory result generated by a laboratory scientist. I encourage laboratory scientists to specialize into more vibrant fields like virology, infectious diseases



Nancy Bowen in Nairobi, Kenya. (Source: Nancy Bowen.)



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Citation

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Pathophysiology of COVID-19-associated coagulopathy and its impact on laboratory measures of coagulation

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes COVID-19, which has ravaged the world since January 2020, infecting and killing millions of people worldwide. Based on the total number of globally infected individuals, approximately 2% of confirmed SARS-CoV-2 infections succumb to the disease. The infection may be asymptomatic or may cause a broad range of symptoms, including, but not limited to, mild symptoms of the upper respiratory tract, cytokine storm, multi-organ failure, life-threatening sepsis and COVID-19-associated coagulopathy causing serious thrombotic complications. The exploration and understanding of the mechanisms behind the severe course of COVID-19 is crucial to improve treatment, recovery, and ultimately, survival rate of hospitalized patients. Laboratory parameters are not only essential to better understanding the physiological mechanisms of the disease but also to monitor disease progression, evaluate the effectiveness and success of treatment.

The cytokine storm

An early sign of severe COVID-19 and a predictor for worse outcomes is the occurrence of the cytokine storm. A cytokine storm is an unregulated and excessive release of pro-inflammatory cytokines, first locally in the infected lung and later systemic throughout the body.¹ High plasma levels of inflammatory markers such as C-reactive protein (CRP), serum amyloid A (SAA), ferritin, procalcitonin, and cytokines (e.g. interleukin-6 (IL-6), interleukin-10 (IL-10) and tumour necrosis factor- α (TNF- α)) are indicators of a hyperinflammatory response and an underlying cytokine storm.^{2,3} The increase in pro-inflammatory cytokines, in particular, IL-6, TNF- α , and IL-10, which are elevated

in patients with COVID-19, are indicators of a cytokine storm and are associated with disease progression and outcomes in severe COVID-19 patients.^{4,5} Currently, it is unclear if immune hyperactivity, dysregulation of the inflammatory response to the viral infection or immune dysregulation causes the progression to severe COVID-19.¹

COVID-19-associated coagulopathy

The cytokine storm with its excessive release of pro-inflammatory cytokines may also play a key role in the pathophysiology of COVID-19-associated coagulopathy by activating endothelial cells and leukocytes, in particular neutrophils, which in response produce neutrophil extracellular traps (NETs), a process called NETosis. NETs promote thrombus formation and amplify cytokine production and have been identified to play a significant role in the pathophysiology of COVID-19.⁶ In addition to the activation of endothelial cells and neutrophils, the direct interaction of the virus with the contact system, part of the innate immune system, specifically with that of factor XII (FXII) and plasma prekallikrein may also contribute to the highly prothrombotic environment at the site of infection.⁷ The formation of activated FXII via SARS-CoV-2 contact may not only initiate thrombosis via the intrinsic pathway of coagulation (e.g., increase thrombin generation, fibrin formation (microthrombosis), fibrinolysis, and increased D-dimer levels), but also the production of bradykinin (increases vascular dilation), and increases vascular permeability. Thus, SARS-CoV-2 directly and indirectly influences the coagulation system, creating a highly prothrombotic state in COVID-19. **Figure 1** schematically summarizes the pathophysiological



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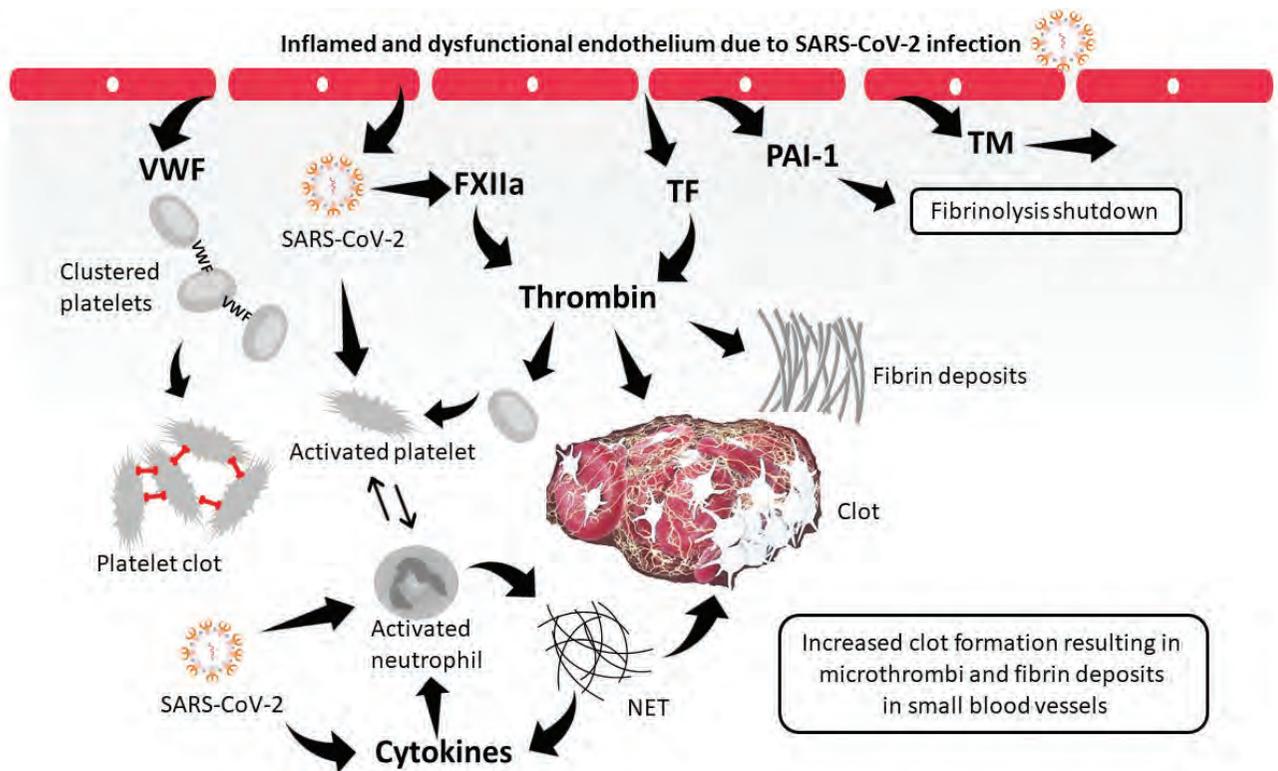


Figure 1. Scheme of the pathophysiological mechanisms of COVID-19-associated coagulopathy.

the highly prothrombotic state in COVID-19 patients causes an unprecedented range of thrombosis-related disorders in affected patients. From benign skin lesions on the feet (e.g., COVID toe) to life-threatening thrombotic events, the SARS-CoV-2 virus has demonstrated a strikingly high prevalence of deadly blood clots. Early studies have shown that approximately 25-45%⁹⁻¹¹ — or even up to 70%¹² — of critically ill patients have a confirmed venous thromboembolism (VTE) (e.g., deep vein thrombosis (DVT) or pulmonary embolism (PE)), and approximately 70% of COVID-19 patients who died had met the International Society of Thrombosis and Haemostasis (ISTH) criteria for disseminated intravascular coagulation (DIC).¹³ Analysing available study data, the weighted mean prevalence of VTE was found to be as high as 31.3% in COVID-19 patients¹¹, while the pooled incidence of VTE in COVID-19 patients admitted to the ICU was 28%.¹⁴ The incidence of VTE can steadily increase in hospitalized patients

during severe COVID-19, from 16% after 1 week to 42% after 3 weeks.¹⁵ When comparing those findings with incidence of VTE in patients with pneumonia following respiratory tract infections, the rate of VTE in COVID-19 patients is 7- to 8-fold higher.¹¹

An autopsy on 12 deceased COVID-19 patients revealed DVT in 7 of 12 patients (58%), while PE was the direct cause of death in 4 patients (33%).¹⁶ A histological analysis of pulmonary vessels in COVID-19 patients showed thrombosis and endo-theliitis throughout the pulmonary vasculature with alveolar capillary microthrombi being ninefold more prevalent in COVID-19 patients than in patients with H1N1 influenza.¹⁷ The high incidence of thromboembolic events in COVID-19 patients, which are also frequently the cause of death, highlight the importance to diagnose, and treat COVID-19-associated coagulopathy. One of the most relevant laboratory parameters to diagnose and monitor COVID-19-associated coagulopathy is the determination of plasma D-dimer

levels. Other laboratory parameters of coagulation are also altered in COVID-19 patients please see **Table 1**.

Following a COVID-19 diagnosis, haemostasis testing, monitoring, and therapy have been shown to play a decisive role in COVID-19 patient management.

D-dimer – a primary marker for COVID-19-associated coagulopathy

Elevated D-dimer levels were found to be a crucial laboratory marker to indicate a thrombotic risk in COVID-19 patients.^{18,19} However, when interpreting D-dimer results, several aspects must be considered. For example, D-dimer levels can increase with age and are elevated during pregnancy.²⁰ In addition, high plasma D-dimer levels are also observed in a variety of clinical conditions including but not limited to DIC, sepsis, inflammation, DVT/PE, immobility, liver disease, malignancy, recent surgery, preeclampsia, and trauma. D-dimer is primarily used to rule out DVT/PE in low risk-

Impact on Virchow's triad in COVID-19 associated coagulopathy

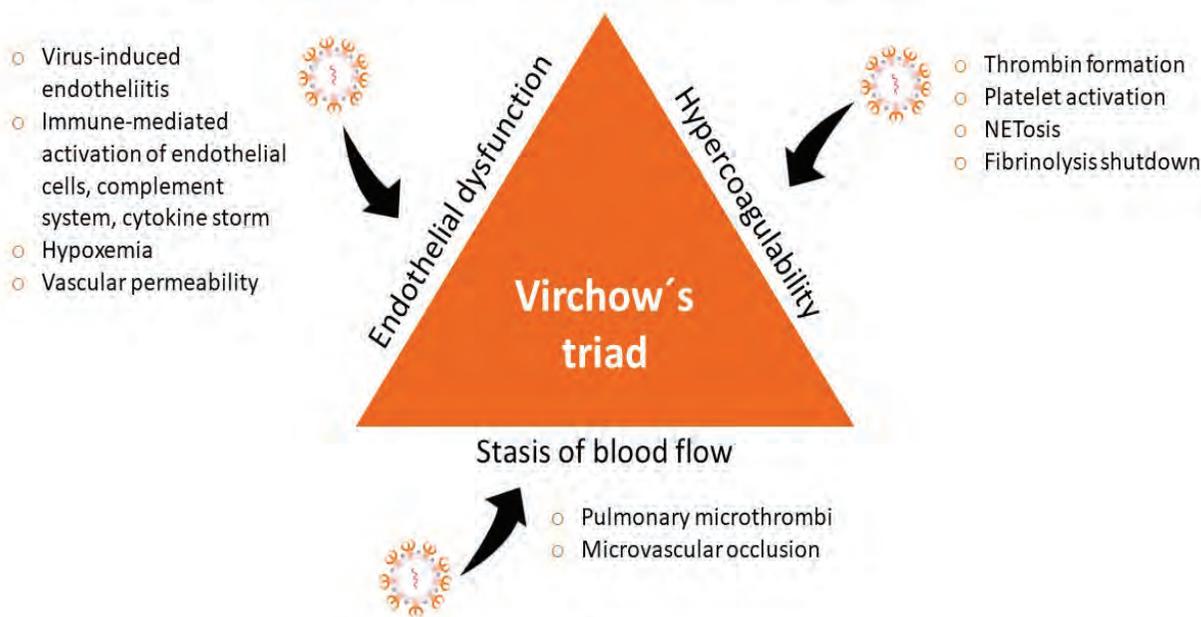


Figure 2. The impact of SARS-CoV-2 infection on Virchow's triad of thrombosis

patients (non-hospitalized) due to its high negative predictive value, and to diagnose and monitor DIC in conjunction with other laboratory parameters. It is also important to note that D-dimer is not a clearly defined antigen. It consists of multiple D/E-fragments of different molecular weights. Thus, the D-dimer antigen is heterogenous, as are the antibodies used to measure it; therefore, the D-dimer assays cannot be standardized to an international standard yet. Each assay uses its own calibration material, which means comparing or transferring D-dimer results has to done with great caution. Some assays use fibrinogen equivalent units (FEU), while other assays report in D-dimer units (DDU). D-dimer results are more commonly reported in FEUs (FEU = 2xDDU).

One of the first reports highlighting the importance of D-Dimer was a study of 191 hospitalized COVID-19 patients in Wuhan (137 survivors, 54 non-survivors), which identified elevated D-dimers levels greater than 1 µg/mL FEU (odds ratio:

18.42, 2.64–128.55; p=0.0033) on admission as a strong predictor of in-hospital death.²¹ Another retrospective study from Wuhan, China, looked at 343 COVID-19 patients, of whom 330 survived and 13 died.²² A D-dimer cutoff of 2 µg/mL was derived by receiver operator characteristics (ROC) curve analysis which yielded 92.3% sensitivity and 83.3% specificity in predicting in-hospital mortality. In addition, using Kaplan-Meier curves, patients with COVID-19 with D-dimer levels >2 µg/mL FEU on admission were shown to be 50 times more likely to die than patients with D-dimer levels <2 µg/mL FEU.

Comparable results regarding the D-dimer cut-off and its predictive power were found in a study on 248 hospitalized COVID-19 patients with 17 non-survivors.²³ ROC curve analysis revealed a cutoff of >2.14 µg/mL FEU of D-dimer on admission to predict death with an odds ratio (OR) of 10.17 (95% CI 1.10-94.38, P=0.041).

Another multicentre retrospective study that included 400 hospital-

ized patients showed that an elevated D-dimer >2.5 µg/mL at initial presentation was predictive of coagulation-associated complications during hospitalization, including thrombosis, bleeding, critical illness, and death.¹⁹

As increased D-dimer levels are common in COVID-19, the exclusion or diagnosis of VTE using plasma D-dimer may need to be adapted. The widely used cut-off for the exclusion of VTE in non-COVID-19 patients of <0.5 µg/mL FEU is not suitable. A study analysing VTE in 100 COVID-19 patients admitted to the intensive care unit (ICU) calculated an optimal cut-off for the exclusion of VTE of <2.0 µg/mL applying ROC curve analysis to their data set.²⁴ However, a cut-off value of >8.0 µg/mL provided an optimal sensitivity and specificity for the diagnosis of VTE in COVID-19 patients. The authors conclude that those two D-dimer cut-offs may be useful to identify patients with a low or high probability for the presence of VTE.

The above studies indicate that D-dimer can be used as an early

prognostic marker for COVID-19 progression including mortality and thrombotic complications as well as a helpful marker to improve management and outcomes in COVID-19 patients.

Other markers of COVID-19-associated coagulopathy

Although D-dimer has been used extensively as a laboratory marker in COVID-19, other laboratory markers of coagulation are also altered.²⁵ For example, prothrombin fragment 1+2, an early indicator of thrombin formation, was found to be markedly increased in COVID-19 patients.²⁶ In addition, fibrinogen, von Willebrand Factor (VWF) and factor VIII (FVIII), haemostasis-associated acute-phase reactant proteins, are also elevated in COVID-19 (Table 1).^{25,27} Fibrinogen levels are increased in hospitalized patients due to hyper-inflammatory response.¹⁹ However, early studies have shown a markedly reduced fibrinogen mimicking levels associated with DIC in patients with severe COVID-19.¹³ The significant

increase in FVIII and VWF not only confer an increase in thrombotic risk in COVID-19 patients, but are also markers of endothelial activation.²⁵

High plasma levels of VWF promote tethering of platelets to the inflamed endothelium, which may lead to platelet activation as shown by increased P-selectin expression of platelets isolated from COVID-19 patients (Fig. 1).²⁸ Platelets from severe COVID-19 patients were assessed under high shear conditions using the PFA-200 system, which showed decreased closure times compared to those of patients with intermediate COVID-19, indicating that platelets of patients with severe COVID-19 are hyperactive.²⁸

Increased plasma levels of soluble thrombomodulin and plasminogen activator inhibitor-1 (PAI-1) have also been reported.²⁵ Only thrombomodulin bound to the extracellular membrane of endothelial cells can convert activated thrombin (FIIa) from being prothrombotic to being antithrombotic. An increase in soluble thrombomodulin means

a decrease in membrane-bound thrombomodulin and its ability to attenuate clot formation. PAI-1 inhibits fibrinolysis, the endogenous process resolving blood clots; however, high concentrations, as seen in inflammatory responses, can tip the balance of coagulation in the direction of thrombosis.

Furthermore, Nicolai and colleagues²⁸ evaluated the formation of neutrophil extracellular traps, or NETosis, in patients with COVID-19. Conducting an experiment in which platelet-rich plasma isolated from either healthy donors or COVID-19 patients was incubated with control neutrophils, and analysing the formation of NETs by confocal microscopy, an enhanced NETosis was noticed in severe COVID-19 patients.

The alteration of all those coagulation parameters in plasma are pointing in the same direction: COVID-19-associated coagulopathy is a hypercoagulable and highly prothrombotic state requiring thorough treatment and monitoring.

Laboratory Coagulation Parameter	Change in COVID-19	Indication
D-dimer	↑↑	Increased clot formation
Prothrombin time	↑	Unbalanced extrinsic coagulation
Fibrinogen	↑ (acute phase) ↓ (DIC phase)	Inflammation DIC
Platelet count	↓/↑	Increased platelet consumption
Von Willebrand Factor (VWF)	↑↑	Endothelial dysfunction and platelet activation
Coagulation Factor VIII	↑↑	Thrombotic risk
Plasminogen Activator Inhibitor-1 (PAI-1)	↑↑	Endothelial dysfunction/fibrinolysis shutdown
Prothrombin fragment 1+2	↑↑	Increased clot formation
Soluble thrombomodulin	↑↑	Endothelial dysfunction/decreased anticoagulant activity of endothelium

Table 1. Significantly altered laboratory parameters of coagulation and their indication in COVID-19

Therapy and monitoring of COVID-19-associated coagulopathy

Various societies and expert groups have issued treatment and monitoring recommendations for COVID-19-associated coagulopathy.²⁹⁻³³ Daily measurements of D-dimer and fibrinogen levels, prothrombin time (PT), and platelet count are indicated to detect and monitor COVID-19-associated coagulopathy as well as success of anticoagulant therapy. Anticoagulation with prophylactic to therapeutic doses of preferably low-molecular weight heparins (LMWHs) or unfractionated heparins (UFH) is strongly recommended. Dosing depends on disease status and risk profile of the patient.²⁹⁻³² Therapeutic monitoring of the heparins using anti-FXa-assays but not the APTT (activated partial thromboplastin time) is preferred. Anticoagulant therapy success may be monitored using plasma D-dimer levels.

Several clinical trials are currently underway to help optimize treatment protocols from drug dosing, application timing, and the choice of the right anticoagulant drug(s) and other potentially helpful drugs (e.g., the antiplatelet drug clopidogrel, tissue plasminogen activator (tPA), thrombomodulin, antithrombin). Anticoagulation predominantly with LMWH is now standard of care for hospitalized COVID-19 patients. But the high incidence of thrombotic complications in COVID-19 despite anticoagulation with LMWH clearly shows that there is still a lot room for improvement in treating and managing COVID-19-associated coagulopathy.

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INTRODUCING THE LABORATORY NETWORK LEADERSHIP AND MANAGEMENT COURSE

There is no formal training in leadership and management for the coordination of a national tiered laboratory network. The lack of comprehensive training on concepts and methodologies for network improvement hampers the advancement of laboratory services as a whole.

ASLM, Clinton Health Access Initiative, Foundation for Innovative New Diagnostics (FIND), and other partners have developed a laboratory network leadership and management course. The course will introduce concepts and activities essential to adequately design, optimise, lead and manage functional, high-quality laboratory networks. The course is part of the ASLM Laboratory Systems Community of Practice (LabCoP) program and focuses on human health laboratory network management. The course is designed to complement the WHO Global Laboratory Leadership Program (GLLP) in Africa.

The course will tour from country to country. Members of national laboratory technical working groups or similar, representatives of selected regional laboratories, and future laboratory leaders are encouraged to participate. Participants will work in groups to improve the laboratory network capacity in their country.

After this course participants will be able to:

- Explain the importance and potential benefits of a functional and well-coordinated national laboratory network.
- Contribute to the development and optimization of the laboratory network in their home country using evidence-based approaches.
- Contribute to the implementation of the tiered-laboratory-networks planning cycles such as preparing, implementing, monitoring and evaluating tiered-laboratory network-related national laboratory policies, strategies and action plans.
- Manage and supervise the laboratory network in their own country using appropriate soft skills.... and more.

The course will consist of five phases over a 9-month period that include individual and group assignments, face-to-face training, and a final assessment. The [ASLM Academy](#) will issue a certificate of completion at the end of the program.

Interested countries should submit a letter from the Ministry of Health supporting their participation in the course, and identify its members of the National Laboratory Technical Working Group or similar and other potential participants. The maximum group size per country is 25.

For more information, please contact [Dr Collins Otieno here](#).