MakSPH virtual seminar 22nd April 2020

Pharmaceuticals and health commodities in the COVID-19 response in Uganda: quality assurance, access and best practices

Chair: Dr. Peter Waiswa, Associate Professor, School of Public Health, College of Health Sciences, Makerere University

Panellists:

1. Dr. Freddy Eric Kitutu, Ag. Dean, School of Health Sciences, College of Health Sciences, Makerere University
2. Ms. Brenda Clare Kitimbo, Principal Regulatory Officer, National Drug Authority
3. Dr. Pauline Byakika, Associate Professor of Internal Medicine, Head of Department of Medicine, College of Health Sciences, Makerere University – also member of COVID-19 Case management scientific committee of Ministry of Health, Uganda.

Opening remarks by Chair

- Welcomed the audience to the webinar and emphasized that this is part of the routine MakSPH Wednesday seminars.
- He gave a background on the number of cases in Uganda (58), most mild and some recovered.
- He mentioned that the population was scared about what would happen if they get infected and asking if there were any vaccines available, treatment, technologies and for ventilators and technologies made locally. He noted that the population wonders whether these are well regulated and certified.
- He said presenters will give an overview of the pharmaceuticals and health commodities in the COVID-19 responses in Uganda. They will highlight issues of quality assurance, access and regulation.
- He went ahead and introduced the 1st panellist: Dr Freddy Kitutu and that he would discuss the available products under investigation for potential COVID-19 use and vaccines.

Remarks by Dr Freddy Eric Kitutu

- He expressed gratitude for the platform to share his expertise.
- Mentioned that the spread of COVID-19 had been rapid over the past months with Uganda having 58 cases. Highlighted how pandemic has revealed our vulnerabilities in terms of access to pharmaceuticals of the desired quality, adding that it has provided a true test of the global medical supply chain.
- He added that it was part of the global debate if the global medical supply chain was able to handle for example with China and India, the main pharmaceutical suppliers, also largely affected.
- Although COVID is a global issue, countries were becoming more nationalistic for example German instructing no exports from their manufacturers until the local need is met.

- He wondered if the sanitizers produced locally were quality-assured, and the need for more diagnostic testing tools and noted that drug quality is vulnerable to fear, desperation and misinformation during the pandemic. He said diagnostics were limited for the start and testing has been generally low due to shortage of testing kits. The PPEs were also limited as many countries could not afford N95 masks for health workers and ventilators and have resorted to ordinary masks. He indicated that since the 2018 Ebola outbreak, shortage in medical supplies and PPE led to increased infections and poor control of the epidemic hence a close eye to the supply chain is necessary. He added that closure of borders has affected the supply of these pharmaceuticals as well.
- He made the following suggestions/reflections:
    - Key actors such as MOH to pay attention to the supply chain for pharmaceuticals. Need to analyse the effect of these restrictions on the flow of pharmaceutical supplies.
    - Government to look at other conditions/essential health services for example if the supply chain with the COVID-19 outbreak is still able to ensure people access other essential health care services.
    - With 80-90% of Uganda's pharmaceuticals imported from China, India and other countries, the effect on the supply chain might not be felt now but would be felt later with years to come, key players need to act.
    - Need to pay attention to the testing trials of products such as chloroquine, hydroxychloroquine, ivermectin, immune-modulators, ARVs: Lopinavir / Ritonavir and Remdesivir in order to understand their role during COVID-19 and also to learn more about the pathogenesis of the disease. So, there is a need to be cautious as we recommend some of these products that have caught media attention as evidence is still sketchy.
- Concerning vaccines, he indicated that oxford has identified potential vaccine candidate with about 80% success rate and is due to carry out tests within the UK in 1 month. Bill Gates continues to be a big advocate of vaccines and so far, has invested money in building 7 factories.

Remarks by Ms Kitimbo Brenda Clare

- Thanked the members and Prof Waiswa for the opportunity to communicate with the people.
- Stated that her focus would be on the regulation of medical devices which she defined as instruments, apparatus, machine or implant that is used in the diagnosis, prevention, monitoring, treatment or alleviation of the disease or anything that supports or sustains life or anything used to disinfect the surgical instrument as well as any implement that is used in the investigation, replacement or modification of support of anatomy.
- For COVID-19 response, NDA mostly focused on ensuring the quality of the pharmaceuticals together with the medical devices and ensuring that they facilitated access of these products to the people that needed them.

- She mentioned focus on four trending products: masks, sanitizers, gloves and diagnostic kits.
- Masks:
    - Mostly used in the prevention and spread of transmission and are classified into 2 types; type 1 and type 2 depending on the bacterial filtration efficiency. Type 2 is further classified into 2: type 2 and type 2R depending on whether the splash resistance test has been done.
    - The regulation focuses on whether the bacterial filtration efficiency has been done, the applicability, microbial cleanliness as well as the splash resistance.
    - Four manufacturers of masks for COVID-19 identified. The role of NDA is to ensure whatever gets to the market is of the required quality, inspection of premises to ensure they meet quality standards for medical devices, testing of quality to ensure that products on market are of good quality.
    - Noted there had been an argument between the N95 and ordinary masks and clarification on this is N95 is considered under the type 2R; used by health care professionals. Type 1 is used by ordinary people.
    - There is currently a shortfall in the labelling of masks and most clients are unable to know what kind of masks to use for example type 1 being used in hospitals. There is thus need for enforcement and education of health care professionals on the kind of masks they need to use. For COVID-19, type 2R and surgical respirators are recommended.
- Sanitizers
    - NDA has adopted the WHO formula but because of the gap most people were producing substandard products and based on surveillance, they realized that out of 45 samples tested, 25 didn't meet the quality parameters and failing in areas of the alcohol content and measures have been taken to ensure these products are taken off the shelves. The public has been notified on the approved sanitizers.
    - The WHO formula contains ethanol 80% v/v or Isopropyl alcohol 75%, hydrogen peroxide 0.125%, glycerol 1.25% and sufficient water.
    - Due to need and demand, NDA opened up to more players/manufacturers as long as they met the minimum quality requirements. Among players included cosmetic facilities, academic institution with laboratories, and distilleries.
    - Requirements looked out for from these manufacturers are: documentation, personnel used and qualifications and labelling. The public are encouraged to report any advance reactions brought about by using these sanitizers.
    - Before COVID-19 response, only 4 manufacturers were notified by NDA but currently, there are 68 people showing interest and 45 have been tested of which 20 have met the quality standard and 25 haven't and have to do corrective action to qualify.
- Gloves both surgical and examination
    - These are used in sample collection, surveillance and screening and they can either be latex, nitrile or vinyl.

    - One of the regulatory controls for gloves by NDA is post shipment load testing before they are used. Tests used is the American standard and in case they don't meet the standard are destroyed.
- Diagnostic kits
    - Classified as class D medical devices and currently, 2 labs are doing PCR based diagnostics one from a facility called "diagin" and another from BGI.
    - The regulatory oversight done by NDA is mostly on safety, accuracy and reliability of these results and anyone who wants to bring in these kits must have validation from UVRI.
    - Role of NDA in the development of these kits is: ensure they meet essential principles for medical devices and NDA assesses their laboratories to offer advice at an early stage so as to meet all parameters
- The other medical devices NDA has been looking at are viral transport media for sample collection, the oxygen delivery devices, patient ventilators, ultrasound scans, nasopharyngeal airways infusion devices.
- Indicated there are serious dangers of using products not approved by NDA; compromised antimicrobial activity especially for sanitizers and toxicity from sanitizers adulterated by ethanol, inadequate protection for cases of the gloves.
- Indicated that more information can be found on the NDA website in terms of guidelines for importers, manufacturers, consumers, innovators and researchers.
- Her recommendation for policymakers was that the National Medical Equipment Policy 2009 be revised to include incentives for manufacturers to build the local industry, including medical devices.
- For innovators, it would be good to engage NDA at an early stage to shorten the review period.
- For professional healthcare workers, it is important to set specifications for what is supplied to the HCs especially medical devices and prioritize PPE.

Remarks by Dr. Pauline Byakiika

Indicated patients in Mulago were under supportive treatment while those in Entebbe had received treatment with chloroquine in addition to supportive care. Noted that:

- Under COVID-19 management, the current standard of care is supportive management. No drugs have been approved yet. However, several studies had tried out different drugs from chloroquine, hydroxychloroquine, Remdesivir and immune modulators.
- As case management committee, despite no drug approved yet, they have advised the use of chloroquine and hydroxychloroquine under the framework of use for emergency settings as well as research and compassionate use.
- In Uganda, patients that have received chloroquine have done well and since chloroquine has been used for several years as a malaria drug and hydroxychloroquine for rheumatoid illnesses. Evidence shows that hydroxychloroquine has a better safety profile than chloroquine and under the compassionate use of drugs, patients can benefit from the 2 drugs.

- Indicated that both drugs have antiviral properties hence interfere with the attachment of virus on receptor sites in the respiratory tracts thus interfere with viral entry and ph-dependent mediated entry and maturation of the viral proteins once they enter the cells and maturation of viral proteins and that they have anti-inflammatory properties hence patients should get it on compassionate terms.
- Two properties make the drugs a better option for patients and can prevent patients with COVID-19 from progressing to severe state so fast and clinicians may not have room to intervene to stop the progression. Therefore giving patients these drugs early may have a benefit of stopping them from progressing to severe cases thus reduce the burden of overwhelming health facilities.
- Stated that some side effects such as cardiac arrhythmias exist but they don't occur in all patients and can be monitored so they have put it in their protocol to benefit patients and reduce the possibility of a high burden of patients that health workers may not be able to treat once in severe and critical illness.
- Other drugs like Remdesivir are at the early research stage and several clinical trials registered but not much literature about it.
- The immune response modifiers have been tried in clinical trials and are currently used in the U.S hospitals. Steroids are controversial with contradictory evidence about efficacy and many studies show that they have effects.
- The other form of treatment is convalescent serum from survivors of COVID-19 which might contain neutralizing antibodies however in Uganda, this has not been adopted although this has been bought to the attention of blood bank. Other countries like the U.S. have already considered this.
- Other forms of therapies put in traetment protocols for supportive therapy include: vitamin C, D and zinc. These enhance the regeneration of endothelium lining and healing.
- BCG vaccination literature compared survival of COVID-19 patients where BCG usage areas were compared to areas with no BCG coverage. However, this had limitations as testing rates in the two populations were different and many different confounders like age no well accounted for.
- Oxygen therapy is very important for health care facilities and NDA should look into pulse oximeters because data shows that some patients don't have all the other symptoms but have deteriorating oxygen saturation (hypoxia) so it is important to monitor oxygen saturation using pulse oximeters and immediately it is realised that their oxygen saturation is going low then they are staretd on oxygen therapy.

Comments, questions and answers

Question: Uganda's cases have been mild. Please comment on why we are getting only mild cases?

Response by Dr Byakika: This is a difficult question at the moment but we know that other factors influence why a patient would get a mild or severe form of the disease. The patient's characteristics for example areas with overwhelming COVID-19 numbers,

patients' characteristics have shown that older patients have more severe disease, patients with comorbidities like hypertension and diabetes have more severe disease and also other characteristics like smoking that upregulates the ACE2 receptors in the epithelium in the respiratory tract and thus increase viral attachment and entry and viral load. So specific characteristics have been found in patients with severe disease and also early intervention is beneficial as it slows down viral replication if you give them chloroquine as it has anti-viral and inflammatory properties and response in Uganda was quite early and thus might be a contributing factor to slowing down progression to a more severe form of the disease.

Question: You said you used chloroquine in Entebbe and Mulago supportive treatment. A lot of discussions and papers have come out questioning these therapies, in your opinion is there a difference between patients in Mulago who did not receive chloroquine and the patients in Entebbe.

Response by Dr Byakika: First, Entebbe hospital did not use hydroxychloroquine but chloroquine while Mulago offered supportive therapy and didn't use chloroquine. However, the majority of the patients in Uganda have had mild disease especially those in Mulago hospital and the major concern was the co-morbidities.

If we don't treat co-morbidities, patients will deteriorate since they are already stressed because they have COVID-19 and many attempts not to adhere to their treatment of comorbidities would not be good and so Mulago hospital physicians stressed management of these comorbidities like diabetes and hypertension. If a patient had uncontrolled diabetes or hypertension, they will go down the drain so the emphasis of management of comorbidities is important. So, this worked well for Mulago and also knowing that patients had mild diseases compared to Entebbe. Some patients in Entebbe had only mild form of the disease but also symptoms but these were well controlled both with supportive therapy and chloroquine. The overall majority of COVID-19 positive patients will be asymptomatic and only a small fraction will come down with symptoms so it's those symptoms that you have to manage but also mental health is very important to take care of.

Question: COVID has shown that we have to be self-reliant and we have a lot of scientists, why aren't we expediting our production of most of these commodities. The young man Mijumbi who was trying to make a therapy. Is it just unethical or someone pretending and how far with his work?

Response by Ms. Kitimbo: we have had an interface with Mijumbi as NDA and we think as scientists you do want to shoot down people's ideas and need to support local innovation as much as we can. We have thus linked Mijumbi to Ministry of Sience and Technology so that he can be guided on how he can improve his claims. The findings were that he didn't have a certified laboratory to carry out his tests and of course, it was hindering him. what we found on the ground was that he was using his residence as a laboratory which was dangerous for him if he was to handle microorganisms like viruses and bacteria.

Question: Can you please comment on homemade masks including do it yourself (DIY) masks?

Response by Ms Kitimbo: currently we have 2 local manufacturers who are making the type 1 masks. The type 1 masks are not for health care workers but ordinary people. The reason for limiting to type 1 is they have not been able to demonstrate the splash resistance. So, without the splash resistance test as well as the durability test the mask will not be able to qualify for use by health workers.

Response by Dr. Kitutu: We know masks are supposed to prevent the transmission but as mentioned, they are of different filtration abilities but during COVID, the masks should be able to cover both the nose and mouth due to known route of transmission as mucus membranes. Again the recommendation for masks have taken in consideration the logistical issues and the N95 can not be provided to the general public due to limited supplies. For MOH, the PPE for COVID need to be prioritised than previously where there was improvisations for health workers.

Question: Are the reusable masks subject to NDA regulations?

Response by Ms Kitimbo: No. as NDA we do not consider reusable cloth masks as medical devices as they are taken as ordinary cloth. This is because the majority of manufacturers are making them from their homes so the facilities used to make them don't meet the quality management standards of production. So, you can't guarantee bio-burden and microbial cleanliness of these devices, they won't be able to do the bacterial filtration test. So, we advise them to advertise and market them as masks used by the general public because according to CDC, any barrier is better than no barrier at all especially for people moving around in public places.

For efficiency of these masks, we look at bacterial filtration efficiency where the type 1 should not be less than 95%, type 2 not less than 98%, for the breathability type 1 and 2 should not be less than 40%, for type 1 splash resistance is not required and microbial cleanliness should not be more than 30 cfu per gram.

Regarding capacity to test these masks: currently as NDA does not have the equipment to test these masks so they are outsourcing testing to a company in South Africa but of course they have plans to acquire the equipment because they believe it will be cheaper in the long run.

The pulse oximeters are also under NDA but they have no local manufacturer however there are many importers of pulse oximeters. NDA has no national standard for pulse oximeters but they are using an international standard to be able to judge performance.

Question: Are you allowing people to import COVID-19 test kits?

Response by Ms Kitimbo: Currently the testing is centralized and coordinated by MOH so we are not allowing any private players to bring in these diagnostic kits but in the event the policy changes due to plans to increase mass screening, we shall be able to notify the public and private players.

Question: How do we exploit local knowledge because we know the source of this same medicine is plants, animals, microorganisms. What efforts are in place?

Response by Ms Kitimbo: In case any innovators or researchers have a product that they think is viable, we have an innovation and research desk they can get in touch with that we can be able to share knowledge and guide innovators on how to bring their products onto the market. So, the innovation and research desk have a form on our webpage that someone can fill so that you can be helped to develop their product.

Response by Dr. Kitutu: Regarding local manufacturers, this is an opportunity to exploit our local potential but we have to understand that pharmecautical manufacturing is a capital intensive venture, requires alot of money, proper planning and has to be long term. Case studies from WHO prequalified CIPLA quality chemicals that produces ARVs, then there is Parenteral industry in Mukono, probably only one of its kind in East And Central Africa. We can learn from them what works but requires government support, investment and long term planning. We also have good products from our local herbs but not sure we can test them during this COVID given the pandemic potential and our few cases in the country but maybe it would start with other diseases before introducing it for COVID.

Question: Ms Kitimbo, **you said the masks being made locally are not suitable for health care workers and yet we know we don't have enough PPE and we need local production. So, what do those companies need to do in practical terms for them to be able to make the masks suitable for use by health workers?**

Response by Ms Kitimbo: On visiting some of the manufacturers, what we needed them to put in place were some of the quality management systems that can guarantee the microbial cleanliness of these masks. If it is put in place then we can be able to upgrade their masks from type 1 to type 2.

Question: Other studies have shown that hydroxychloroquine could have side effects that could be fatal especially for those who have other preconditions and Dr. Byakika I heard you talk about the benefits but I also wanted a comment on the side effects that could be there especially for those with other preexisting conditions.

Response by Dr. Kitutu: The debate about the safety and efficacy of hydroxychloroquine has just started. Dr Byakiika talked about the findings from Entebbe hospital to be promising. We need bigger randomized studies that take into consideration potential confounding factors.

Response by Dr Byakiika: Hydroxychloroquine and chloroquine have documented side effects including side effects on the eyes and side effects on the heart. However, literature has documented that hydroxychloroquine has a safer toxicity profile compared to chloroquine and the feared side effects currently with hydroxychloroquine are the effect on the heart (cardiac arrhythmias). However currently there are no FDA or NDA approved drugs for COVID-19 and several drugs are currently being studied for COVID-19 in clinical trials around the world and most regulatory authorities have indicated that because there is insufficient clinical data to recommend for or against using chloroquine or hydroxychloroquine for COVID-19, the only basis for which a clinician can use these drugs is either under research as a clinical trial under emergency use authorization or

compassionate use where no other option. These have been accepted tentatively but only where a clinician can monitor the patient for these adverse events.

As Uganda, we are going to collect data and analyze it in real-time and inform clinicians and at any point where we realise the toxicity is occurring as the literature is also evolving. If toxicity shows up and it's alarming, we shall have to stop the use of the drug and adopt whatever is coming on next

Question: Wondering whether the universal BCG in our population may have conferred some protection so that most of the cases we have received have all been mild other than severe.

Response by Dr. Kitutu: The BCG claim has been disproved. The initial study as mentioned by Dr. Byakiika was based on national level effect and personally, BCG offers no protection against COVID-19 based on what I have read. The earlier study suffered from ecological fallacy.

Question: I want to inquire about the masks the different types of N95. Is it possible for NDA to come out clearly on what type of N95 mask is useful for our frontline workers?

Response by Ms Kitimbo: We have the N95s and we have different brands, we have those made by Americans, Chinese, Japanese. What the N95 means is that this mask guarantees the bacterial filtration efficiency of up to 95%. It is possible to have N95 masks from different brands but what's common on our market is the one manufactured by 3M. And the one certified for medical purposes is 1860 (green one). The M810 is the dust mask so some tests were not carried out so the manufacturer will not guarantee that the splash resistance will meet the requirements as set out for healthcare workers. So currently on the market there is 1860 (green) and it is what is recommended for healthcare workers. We also have the white ones 3m8210(dust masks) which don't qualify to be used in healthcare settings. Others from china kn95 qualified to be used in healthcare settings.

Closing remarks by Chair

- Stated that the supply chain seems problematic and predicted consequences later since China and India had closed up hence future stockouts of common drugs. Implored policymakers to consider this carefully.
- Issues of the supply chain are quite major and being self-reliant as a country in terms of diagnostic kits, pharmaceutical products and manufacturing is so important and NDA has a big role in regulation and engaging scientists.

Closing remarks by Prof. Wanyenze, Dean, MakSPH

- Emphasized need to work with NDA more and with colleagues from clinical sciences.
- Noted the need to have more products coming from the university to address some of these gaps being discussed. There is need to explore these opportunities and have

more products coming on board. There are also more opportunities for research and innovations that we can do with NDA.

- Highlighted the need to expand these discussions to bring in more people from the College, MOH, those at CDC and hopefully eventually those at the frontline to further bring homegrown African solutions for COVID response.
- Thanked organizers; Esther, Geofrey and Rawlance for coordinating the School webinar series.

Report compiled by: Brenda Wagaba and Solomon Wafula

Reviewed by: Rawlance Ndejjo and Dr. Geofrey Musinguzi.