Title: Insights into the Nigerian COVID19 outbreak

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Abstract : Given the pace of SARS-CoV-2 transmission and its relatively high mortality rate, COVID-19, has the potential to become the most severe pandemic in recent times. This virus's spread across international borders has triggered different responses in countries around the globe with a spectrum of mild, moderate to severe outcomes. Nigeria, Africa's most populous country with many densely populated cities, presents a unique situation for the explosive spread of SARS-CoV-2. However, at the point of this writing, the number of reported confirmed infection and mortality is comparatively lower to other countries with dense urban populations. The exact reasons for this are not clear but include societal, political and infrastructural factors that will influence the course of the outbreak in Nigeria. In this perspective, we have described the ongoing COVID-19 outbreak and its associated peculiarities. We identify critical steps that remain to be taken to contain and control the outbreak in Nigeria.

Keywords: Nigeria, disease drivers, public health, COVID19

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Introduction

Features of the SARS-CoV-2 virus explain it's increased infectivity and transmission rate compared to the SARS Coronavirus and 2002/2003 SARS epidemic. While SARS claimed a total of 8,096 lives and the epidemic was contained by quarantine, the COVID-19 pandemic continues to spread at an alarming pace in some countries, while having been relatively well controlled in others. During the SARS epidemic, South Africa was the only African nation to record a case, while the COVID19 pandemic has so far inflicted a total of 310245 cases [1] across all the countries in Africa.

The first index case in Nigeria was recorded on the 29th February and in less than four months, the confirmed number of infection is over 20000 with 518 deaths reported at the time of writing. For a country with over 200 million, these numbers are low compared to the trends in other parts of the world. This is surprising when you consider the high population density, limited healthcare resources and access and high poverty index and other conditions that are conducive for the spread of COVID-19 in Nigeria compared to a developed country like Germany and Japan. This has given room for the speculation of several unproven factors such as the genetic makeup, presence of some form of endemic innate or adaptive immunity, virus receptor polymorphisms, or environmental factors that may be responsible for the relatively low incidence and case fatality rate in Nigeria. However, the exact reasons for this in Nigeria and different regions of Africa, in general, have yet to be elucidated. Other confounding factors such as availability and access to testing and/or proper clinical management could also be responsible for this.

Here, we described the Nigeria COVID-19 outbreak and the potential factors that might be impacting on the spread and the effect of our intervention policies. We predicted the future of the outbreak in Nigeria and made recommendations for better management of other future outbreaks.

COVID19 Case Distribution; The Nigerian situation

As of June 21, 2020, a total of 115760 cases have been tested in Nigeria with a total of confirmed cases across 35 states and the Federal capital territory. Lagos (8576), FCT (1567), Kano (1190), accounts for the highest numbers of cases with no reported cases in Cross River state. A total of 518 deaths has been reported with a CFR (Case Fatality Rate) of 2.6% with the majority of deaths confirmed in cases with underlying co-morbidities such as diabetes and renal failure [2].

Men accounted for 66% (13318 cases) while females constituted 34% (6926) of the cases with an age-dependent stratification of cases (Fig 1). This suggests a sex and age-dependent predisposition in the prevalence of the confirmed cases. The higher male predisposition was similar to global trends with more males affected than females globally. On the other hand, the age distribution in Nigeria did not reflect the global picture. In Nigeria, young people (31-40) were the most affected population compared to the elderly group (52-78) seen globally [3] (Fig. 2). This was also seen across most African countries like Ghana, South Africa.

The reason for the mean age difference between the Nigerian cases and the global trend is not elucidated, however, we hypothesize that this could be due to the lower median age (a more youthful population) in Nigeria and Africa compared to the US, UK, Italy and other European countries (Fig 2). This lower median age in Nigeria could also influence the outcome and severity of the COVID-19. A high CFR is reported in the countries with an aged population/high median age (Italy, US and UK) compared to the lower CFR in the countries with youthful population/low median age (Ghana, Nigeria, South Africa). The outliers to our hypothesis such as the low CFR reported in Germany and Japan despite their high median age implies the interplay of other cultural, behavioral and socioeconomic factors confounding the outbreak response in these countries and this would require further studies.

Interrogating the Nigeria COVID-19 outbreak response and outcomes.

Following a swift identification and management of the first index case in Nigeria, the government placed a travel ban on 13 countries which had recorded high COVID-19 case numbers [4]. This was followed by a complete restriction of movement in most states by 30th March. However, prior to these measures, there was the formation of the multisectoral Coronavirus Preparedness Group on January 23, 2020, designed to help in risk assessment and improvement of Nigeria's preparedness towards the pandemic. This group was subsequently escalated on Feb 28 2020, to form the national Emergency Operation Centre (EOC) saddled with the surveillance, contact tracing and coordination of COVID-19 response[5,6]. The previously established Public Health Emergency Operations Centers (located in 23 of 36 states in Nigeria) were also activated to coordinate state-level outbreak response (Fig 3). As part of measures to limit social gathering, other major national and local activities within the country were also cancelled. Various economic interventions were also set in place to minimize the impact of the pandemic on the economy, businesses and the people's welfare, employment and job security and to ensure compliance. Notable among these economic interventions was the Central Bank introduction of the guidelines for the operations of the N100 billion credit support for the health care sector (CBN), lifting of cheque clearing suspension to ease payment [7] among others.

Despite all of these interventions, there were still issues with compliance in various part of the country including anti-lockdown protests, increase in crime rate and civil disobedience as unintended consequences of the lockdown and travel restriction [8,9]. This was similar to various anti-lockdown protests reported in Rwanda, South Africa, and other countries partly due to the economic impact of the lockdown [10-13]. In addition, the conflating influence of various enabling and disabling factors such as the demographic (youthful population), sociocultural structure (cohesive communities), poverty and economic issues and the high prevalence of other comorbidities (malnutrition, malaria, HIV/AIDS and tuberculosis) has made the consideration of the local context important for effective response in Africa. For example, in Senegal, a contextualized testing approach taken with the development of their $1 kit per patient antigen detection kit has also helped in their national response. Similar creative and contextualized approach has also been seen in the Madagascan response to the COVID-19 outbreak with the Madagascar "cure" (a herbal blend of the *Artemisia annua* plant). These two approaches (while currently being tested) have shown the importance of a consideration of the local socioeconomic context in offsetting the huge economic cost of testing (using real-time PCR) and pharmaceutical investment. We believe this highlights the need for the customization of outbreak responses to suit the local strength, socio-economic and cultural context.

Also, we analyzed the scenario in Nigeria in comparison with other closely related African countries (data not shown). In this analysis, we observed that despite the increase in daily confirmed cases in Nigeria and these other countries, progressive relaxation of the lockdown started even during the logarithmic phase of the outbreak. This suggests to us that most countries in Africa show a reactive response with subsequent scale-up of responses as the cases increased. We believe that such reactive responses could have been avoided and instead a more proactive approach involving an early imposition of air travel restriction would have significantly helped in reducing the number of imported cases and the subsequent community spread of the disease.

Furthermore, the testing capacity in the early phase of the outbreak was poor and contact tracing response was inadequate. As at 28th March, a month after the identification of the index case and about 100 confirmed cases scattered across 12 states in all the six geopolitical regions, Nigeria and NCDC had only activated 6 molecular diagnostic labs for COVID-19 testing. It took

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another one month for our testing capacity to exceed 2000 per day. The delay in testing and contact tracing, the limited availability of testing material and other logistic issues could have contributed to our transition from imported COVID-19 cases to community transmission in some states.

Prediction and Modeling of the Nigerian CoVID19 outbreak

Here, we used the age-stratified SEIR (susceptible-exposed-infected-recovered) model as described by Noll et al. (2020) [14] to predict and model the Nigerian COVID19 outbreak. The model includes the effect of mitigation strategies based on their duration and 'effectiveness'. Their effectiveness is a measure that quantifies the multiplicative effect of the intervention on the transmission rate. In this model, we chose three effectiveness categories which are 0-20% (low effectiveness), 40-60% (moderate effectiveness) and 80-100% (high effectiveness). We also considered the effect of the duration of the intervention within the different effectiveness categories (1 month, 3 months and 6 months) from the earliest start date of the lockdown in Nigeria (30th March 2020).

It is important to note however that the COVID-19 situation in Nigeria is fast evolving and it is difficult to ascertain the efficacy of the mitigation measures. In addition, this is only a prediction and comes with a level of uncertainty, uncertainty in the parameters and the simplification of the SEIR model might not capture the full complexity of the outbreak in Nigeria. However, this can provide a better understanding of the dynamics of the outbreak and inform government decisions on future impactful interventions.

We obtained certain parameters based on values from studies of the outbreak in China during the early stages of the pandemic. This includes the infectious period of 8 days, and incubation period of 3 days [15] and an estimated Nigerian population of 210 million according to the United Nations projection. We also estimated the annual average basic reproduction number R_0 range of 1.6-3.9

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across settings without mitigation according to values from a study by the Center for Mathematical Modelling of Infectious Diseases (CMMID) [16] and a simulation time range of 1 year from 27th February 2020 to 27th February 2021.

We observed from our modelling results (Figure 4) that Nigeria is still relatively at the early stages of the outbreak and the expected trajectory is dependent on the mitigation measures put in place to contain the spread of the disease. Furthermore, the least duration of an intervention in this study was set at one month with varying levels of effectiveness. From our results, it appears that for the one-month duration model, even with highly effective mitigation measures (i.e. 80% - 100% effectiveness), the number of infectious individuals remains relatively high (Fig 4). Unfortunately, the lockdown in Nigeria only lasted for about one month and has been eased despite the increase in the daily case numbers [17]. Although it would be difficult to calculate the actual effectiveness of the mitigation measures, what we know is that the lockdown was met with some civil disobedience, hence was of low effectiveness [18]. Therefore, provided testing is greatly increased, we expect a surge in the number of confirmed cases in the coming months.

Possible predisposing factors and drivers of COVID-19 outbreak in Nigeria

The variation in the reported incident and case fatality rate in Africa compared to the European counterparts has given room to several unproven factors as drivers of the COVID-19 outbreak. In this section, we have analyzed some of the leading hypotheses on why some individuals might present with less severe outcomes than others and why some states and regions within Nigeria might have reported fewer cases than others.

Sex and gender-based difference in COVID19 severity

Global trend and data from Nigeria have shown that more males are infected and with more severe outcomes during CoVID-19 compared to females (Fig 2). The reason for this is not clear but several factors have been suggested to explain it. Previous studies have shown that sex hormones have an impact on immune responses with the male sex hormone such as testosterone having a suppressive effect and/or anti-inflammatory effect on the immune response. This difference leads to better and stronger immune responses during infection in females than males [19,20]. Evidence of this has been confirmed in a recent preprint paper showing a more robust T cell immune response which correlated with disease outcome in females compared to male individuals [21]. In addition, another preprint study also revealed a role for androgenic hormones in the regulation of expression of SARS-CoV-2 Receptor levels [22]. Thus, the sex-specific differences seen in Nigeria and reported in other parts of the world [23,24] may, therefore, reflect the general effect of sex on disease outcomes.

Furthermore, other gender-associated differences such as behavioral and social practices have also been linked to gender-associated differences observed during the public health crisis [25,26]. For example, some studies have shown that males partake in riskier, less hygienic practices and general non-compliant issues than their female counterparts [25]. This difference could also be ascribed to cultural and gender roles in Nigeria that expect men to be fend and take care of their family and therefore are more likely to expose themselves to disease while in search of the daily meal for their family.

ACE2 polymorphism

ACE2 is the known receptor for entry of SARS-CoV-2 virus. It is mostly expressed in the lung, the kidney, the intestine and the brains. Expression of this receptor at various sites determines the predilection site, transmission, pathology and symptoms of COVID-19. A few reports have noted genetic variation between the ACE2 expression in Africa compared to the Asians and

Caucasians [27]. Genetic association to disease susceptibility in Nigeria is not new, Andersen et al reported a mutation in the LAMP gene that confers resistance to Lassa fever infection on the Yoruba tribe in Nigeria [28].

Therefore, future studies that will explore the role of immunogenetics and diversity in the expression of ACE2 receptor in Nigeria may explain some of the state and regional differences in incidence rates of COVID19 across the country.

Trained immunity

The concept of trained immunity is currently being debated as a possible reason for the low incidence of COVID19 in Nigeria and Africa. This concept is associated with the idea that constant exposure to pathogens makes a critical arm of the immune system (innate immune system) more primed to be able to respond quickly and faster to different pathogens including viruses. This has been reported for examples in countries where BCG vaccination is practised [29]. Therefore, questions as to whether this is true or not while actively being debated needs to be explored. For example, are innate cells from individuals in Nigeria, such as dendritic cells and macrophages, more capable of rapidly producing protective effector cytokines than in other regions with lower exposure to infectious disease? This concept of "trained immunity" previously reported in other cases [29,30] would be interesting to examine in Nigeria.

However, this could be a two-prong situation, where concurrent infection with other pathogens such as worms (which is not uncommon in Nigeria) could have an immunoregulatory effect on the production of optimal effector responses to viral responses[31]. This immunoregulatory effect of co-infection with worms could either be helpful, as this could help delay the cytokine storm that has been ascribed to fatal outcome in some COVID19 cases [32] or be detrimental as it could suppress critical viral immune responses[33]. However, whether there is any beneficial or detrimental effect on this remains to be fully explored.

Weather and climatic conditions

Furthermore, the weather has been posited in some quarters for possible lower prevalence rate in tropical regions versus more temperate regions. The difference in temperature has previously been reported to have an effect on the stability of SARS-CoV-2 [34]. For example, the virus was reported to be very stable at a lower temperature compared to higher temperature [34]. However, questions surrounding whether variation in weather conditions could explain some of the different incidence rate seen in the West Coast of the US versus the East Coast around April is yet to be fully explored. Data from Nigeria comparing Lagos (with an average temperature of 33^{o}) and Kano States (with an average temperature of 38.2^{o}), two highly populated regions suggest that social distancing might be more effective in limiting the spread of the disease than the influence of weather on virus survival. There was no significant difference in the incidence of disease in the two states despite the extreme weather conditions in Kano state compared to Lagos State [2]. Therefore, suffice to say that in Nigeria variation in weather and climatic conditions seems not to affect the spread of the virus but this data still needs to be adequately assessed.

Mistrust and Mis-/Disinformation

An important driver of the spread of COVID19 in Nigeria has been public mistrust of the health system, case reporting and government narratives about the COVID19. This mistrust has been an offshoot of an initial widespread dismissal of the reported cases in Nigeria as a “disease of the elite” and an embezzlement ploy for allocated COVID19 response funds. This was further reinforced by various mis-/disinformation, infodemic and conspiracy theories about the outbreak emanating from various traditional and online media sources. The consequences of this mistrust were reflected in the various civil disobedience and non-compliance with stipulated lockdown rules and social distancing restriction which potentially undermined the impact of the government containment response. This is similar to the previously reported impact of institutional mistrust and misinformation as important drivers of the 2018-19 Ebola outbreak in Congo [35,36].

Other social dynamics with overarching impact on COVID19 health-seeking behaviour and advisory compliance in Nigeria also include the knock-on psychosocial impact of the outbreak as reflected in the forms of fear, anxiety, stress, paranoia, and breakdown of social support structures[37]. This further highlights the need for strengthening the psychosocial response (towards mental health promotion) during outbreaks as opposed to the albeit overt medicalization of responses targeting solely the pathophysiological aspect of the outbreak [37].

Consequence and impact of COVID-19 on Nigerian public health infrastructure

The incidence and spread of COVID19 in Nigeria have led to both positive and negative impacts on Nigerian public health facilities. With travel bans, decreased international trade and increased pressure on national epidemiologic units, an impact on public health infrastructure is inevitable.

One of the consequences includes an effect on other infectious diseases in Nigeria. For example, an evaluation of the Lassa fever epidemiological trend over the past 5 years (2016 – 2020) of the same reporting period (week 1 – 23) also indicates the highest case peak reported in 2020 [38] (Fig 5). While this surge in Lassa fever cases might not be absolutely associated with the current COVID-19 outbreak, the impact of the COVID-19 outbreak would undoubtedly influence resource allocation and the working capacity of the national public health infrastructure. This suggests that effect of the current pandemic would affect the epidemiology and response to the other endemic and integrated disease surveillance and response (IDSR) priority diseases (such as CSM, Cholera, Measles, Lassa fever and Yellow Fever).

On a positive note, the COVID-19 outbreak has brought improvement in the health sector in Nigeria. For example, there has been an increase in the implementation of collaborative One-health approach in the response to COVID-19. This has been illustrated with the incorporation of veterinarians and environmentalists in the Joint Task Force in response to COVID-19 [39]. Furthermore, there has been rapid scale-up and activation of various standalone laboratories to join the reference laboratory network for molecular testing which in the long run would potentially improve the diagnostic infrastructure for other diseases aside COVID-19. From 3 molecular testing centers, we now have 30 testing centers capable of molecular diagnosis of COVID19 [2]. The COVID-19 outbreak has also highlighted the enormous potential for genomic surveillance in Nigeria. ACEGID, Redeemer's University, Ede, in collaboration with the NCDC provided the sequence of the index case in Nigeria within 72 hours of detection. This is an unprecedented turnaround time which informs management and intervention policy in the country. As at today, ACEGID has provided about 20 sequences from the Nigerian outbreak highlighting increased mutation in the spike protein that is associated with severe pathology.

Conclusions and Future Directions

The COVID-19 outbreak like other infectious disease outbreaks has exposed the fragile health system in Nigeria. Though the outbreak is still in its early phase, the lack of adequate testing, the poor health infrastructure, suboptimal investment and funding in the STEM field and lack of properly trained health professionals leave Nigeria in an unknown trajectory.

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In this review, we have described the COVID-19 outbreak from the Nigeria perspective, interrogated the intervention policies by the Nigerian government and predicted the future of the outbreak using the SEIR model. We have also used scientific analysis to discuss potential factors surrounding the COVID-19 outbreak and suggested future critical areas for research.

Finally, as we all work towards returning to normal, we opined that our leeway out of the COVID-19 outbreak and other future outbreaks will require improved diagnostic capacity, effective test and tracing and massive investment in research and health infrastructures.

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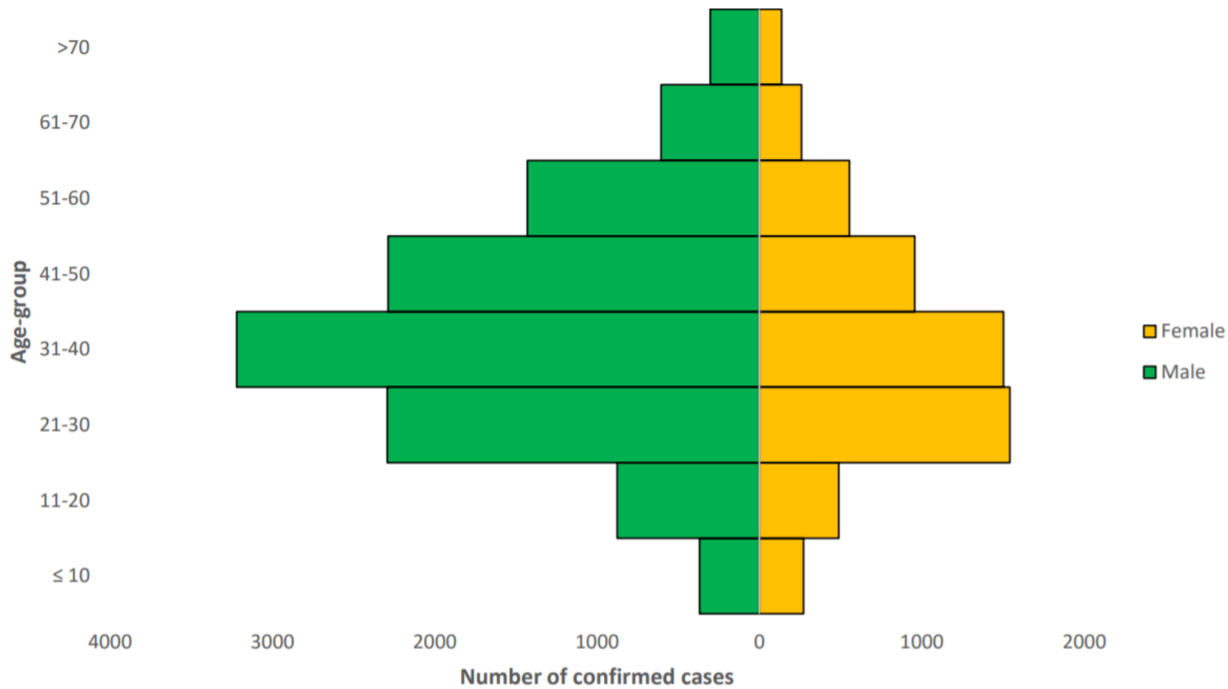

Figure 1. Sex and Age-Group Distribution of COVID19 Confirmed Cases in Nigeria (Source: COVID19 Situation Report 113)[2]

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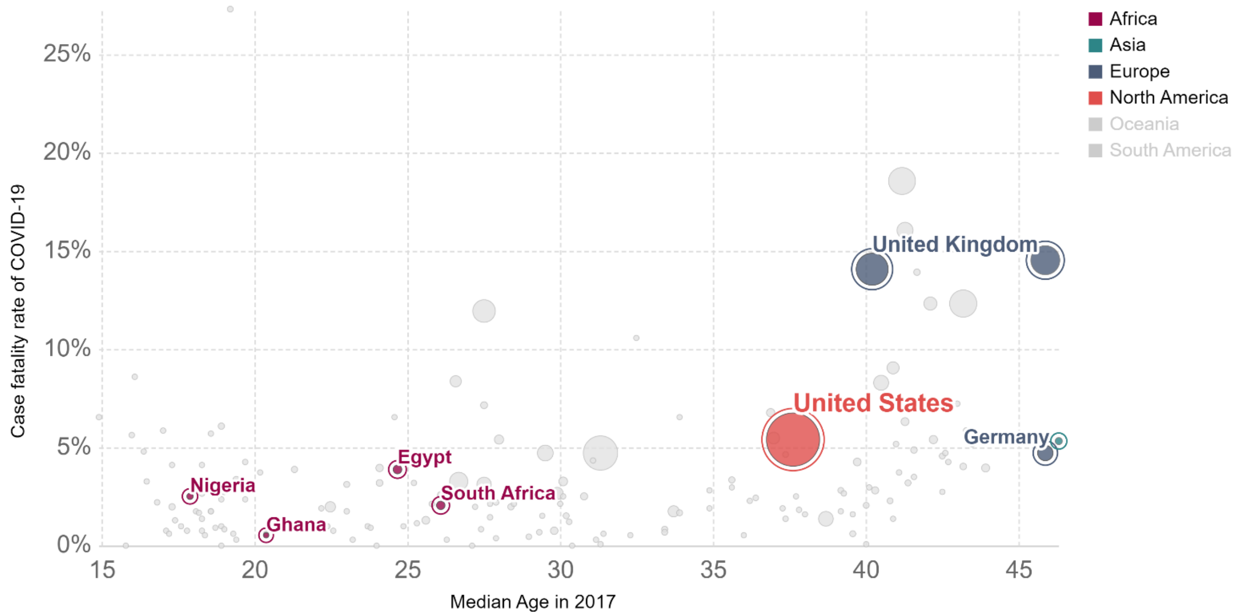

Figure 2. Comparison of the case fatality rate vs median age across different countries using data from COVID19 epidemiological data from Jan 19, 2020 to June 20, 2020. Size of the bubble represents the magnitude of total confirmed CoVID19 deaths up to June 20, 2020 (Data Source: European CDC Situation Update; UN Population Division, World Population Prospects, 2017 Revision. Retrieved from: Max Roser, Hannah Ritchie, Esteban Ortiz-Ospina and Joe Hasell (2020) - "Coronavirus Pandemic (COVID-19)". 'https://ourworldindata.org/coronavirus' [Online Resource]

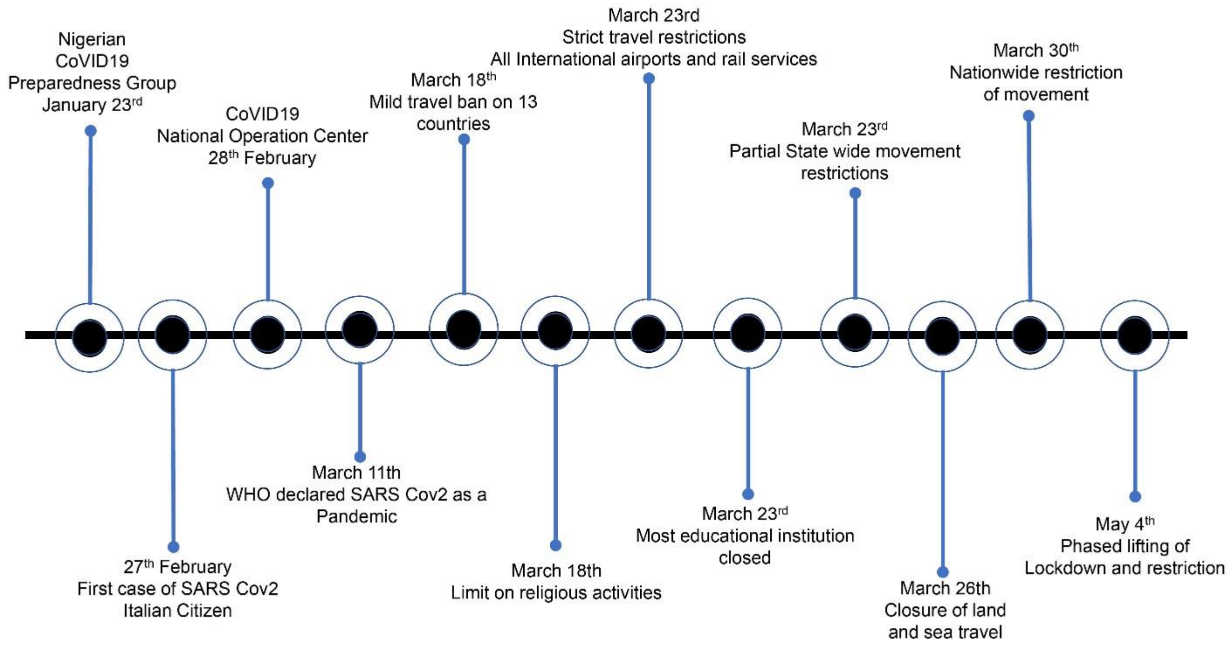

Figure 3. Timeline showing key Nigerian COVID19 response

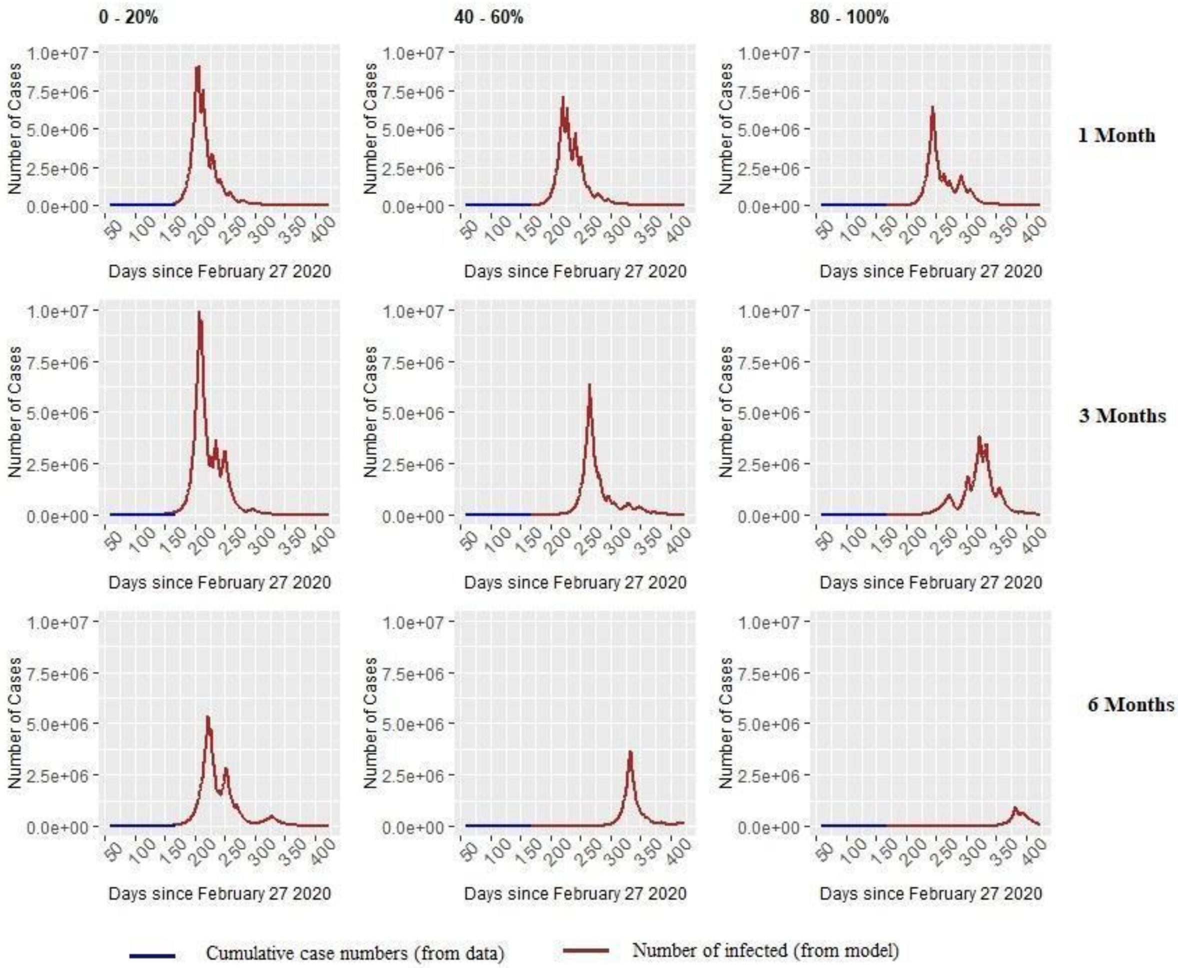

Figure 4. Modelling result of COVID-19 epidemics in Nigeria with different mitigation scenarios from the lockdown start date of 30th March 2020. Cumulative case numbers from 27th February to 14th June 2020. (Data Source: European CDC Situation Update). In the SEIR model, the population is age-stratified into compartments of ICU overflow (O), dead (D), infected (I), susceptible, (S), exposed (E), hospitalised (H), critical (C) and recovered (R) according to Kermack et al. 1927[40].

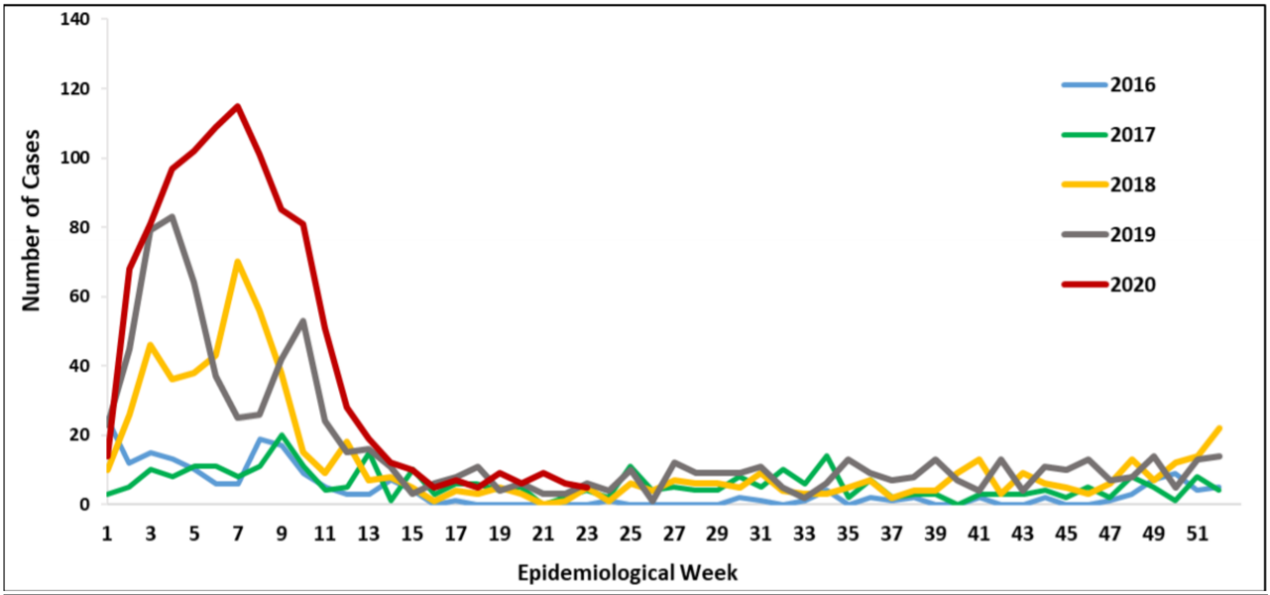

Figure 5. Comparison of the confirmed Lassa fever cases by epidemiological week (2016 - 2020) (source: NCDC Lassa Fever Situation Report - Epi Week 23[38]