Surveillance and epidemiologic evaluation of COVID-19 in Kenya (SEECK)

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2 Lay summary

Lay Title: Understanding the distribution, management and outcomes of COVID-19 in Kenya

Formal Title: Surveillance and epidemiologic evaluation of COVID-19 in Kenya (SEECK).

What is the problem/background?

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by a recently identified virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 has also been referred to as the 2019 novel coronavirus (2019-nCoV). The disease was first identified in late 2019 in China, and has since spread globally, resulting in more than 10 million infections and more than 500,000 deaths as of 1st July 2020. In Kenya, the first case of SARS-CoV-2 infection was reported on 13th March. Since then, the number of confirmed cases steadily rose to more than 6,000 by 1st July 2020. The Ministry of Health has established an Emergency Operation Centre (EOC) to coordinate the technical national response to the epidemic. At county level, Rapid Response Teams implement case identification, contact tracing and isolation. KEMRI-Centre for Geographic Medicine, Coast (CGMRC) has a longstanding partnership with the Ministry of Health, and provides technical support for research and capacity building through four scientific departments: Epidemiology and Demography, Biosciences, Clinical Research, and Health System and Research Ethics. This proposal describes a series of activities aimed at improving the understanding of COVID-19 in Kenya and supporting the national and county emergency response to the COVID-19 pandemic.

What questions are we trying to answer?

Our aim is to collect and analyse data to help understand various aspects of COVID-19 – such as the pattern of COVID-19 cases, the pattern of exposure to COVID-19 among different groups and individual characteristics that may increase or lower the risk of severe COVID-19, how health care is being provided – and to apply this knowledge to guide national planning to limit the negative effects of the pandemic in Kenya. For example, it would be of considerable benefit to the Ministry if they knew the groups of

individuals who are more likely to have poor outcomes and then use this information to plan for control measures to protect these groups. We will investigate questions such as:

- How common is COVID-19 infection in children and adults admitted to hospital and healthy adults such as healthcare workers?
- What proportion of the general population has been exposed to SARS-CoV-2?
- How does COVID-19 affect patients that are undernourished or that have vitamin D/iron deficiency or that are infected with HIV?
- How have hospitals tried to provide routine and COVID-19 related care

Where is the study taking place, how many people does it involve and how are they selected?

We plan to do this work in a range of groups of people across approximately 18 Kenyan Counties. Some of the work will take place in health facilities where we already have approval to work on research projects, such as those listed in Table 2. We will work with the Ministry of Health to identify other sites to collect data based on the priorities identified.

The following individuals will be involved in the various studies:

- **Clinical surveillance of COVID-19.**
  This will include: estimation of the rate of new COVID-19 cases (COVID-19 burden); evaluation of the signs/symptoms, course of illness and outcome of illness and any differences in medically vulnerable children and adults; evaluation of factors that increase or decrease the risk of severe disease and death; and evaluation of the role that shedding of SARS-CoV-2 in stool. **All** adults and children with known or suspected[1] SARS-CoV-2 infection, admitted to study health facilities (see Table 2) and meeting the criteria in Section 9.2.2 will be included. Of these individuals:

[1] **Suspected COVID-19:** Any person presenting with hotness of the body or cough or difficulty in breathing having history of travel from outside the country OR lived with or visited somebody known to have Coronavirus disease (Kenya Ministry of Health. Case definition for novel coronavirus disease (COVID-19) – V25032020. Available from: http://www.health.go.ke/wp-content/uploads/2020/04/COVID-19-Case-Definition-25-March-2020.pdf. Accessed 19 April 2020)

- **All** children and adults who provide consent for clinical follow-up in a cohort as well as consent for collection of blood and stool samples for research over 6 months after admission will be included.
- **All** children and adolescents diagnosed with a rare complication of SARS-CoV-2 infection called “multisystem inflammatory syndrome” will be invited to participate in a study that further investigates that complication.

- **Surveillance for active and past SARS-CoV-2 infection**.
  - Healthcare workers (HCW) at health facilities listed in Section 10.2.1 will be invited to participate. About **1,500** HCW are expected to participate.
  - About 700 other ‘frontline’ workers – in other words, workers likely to be at high risk of being exposed to SARS-CoV-2 or working in jobs important for the functioning of the economy – from approximately 3 companies or sectors such as those listed in Section 10.2.1 will be included. This will be a total of approximately **2,100** non-healthcare frontline workers.
- **Surveillance for past SARS-CoV-2 infection.**
  - 850 adults and children living within health and demographic surveillance systems (HDSS) such as those listed in section 11.2.1 will be selected by chance from lists of residents and invited to participate. This study will be conducted in about 3 HDSS for a total of approximately **2,550** adults and children.
  - Children and adults infected with SARS-CoV-2 but having no systems of recent, new illness (asymptomatic) will be identified from health facilities such as those listed in Section 11.2.2.5. About **200** are expected to be enrolled in the study.
  - Children and adults infected with SARS-CoV-2 and showing symptoms of recent, new illness (symptomatic) will be identified from health facilities such as those listed in Section 11.2.2.6. **All** who meet the criteria listed **will be included.**
- **Understanding the effect on hospitals of COVID-19**
  - Hospital managers, senior and junior clinicians (approximately 20 doctors, nurses, pharamcists etc) will be asked about the changes made in hospitals to help provide care for COVID-19 cases (eg. use of new

equipment or reorganizing of wards) and how they have managed to sustain routine services

- Other studies included in this protocol but not listed above – such as surveillance for past SARS-CoV-2 infection in antenatal clinic (ANC) clients, historical surveillance for past SARS-CoV-2 infection among previously hospitalized non-COVID patients (adults and children), micronutrient testing, genetic testing and studies of how SARS-CoV-2 infection affects how cells function – will not directly enroll participants, but will use samples collected through other studies and activities.

What does the study involve for those who are in it?

- **Clinical surveillance of COVID-19.**
    - Surveillance for the rate of all suspected and confirmed COVID-19 cases (burden of COVID-19) as well as description of the presentation, course, outcomes and risk factors for outcomes in these cases will not directly involve individuals but will instead rely on routine hospital documents that are routinely collected for non-research purposes or national/ County COVID-19 surveillance documents. Use of routinely collected health facility data is approved under separate protocols for clinical surveillance, including waiver of individual consent.
    - The study of the presentation, course and outcomes of SARS-CoV-2 infection in clinically vulnerable patients – such as severely malnourished children, individuals with micronutrient deficiencies, and adults with immunodeficiency or chronic non-communicable conditions – as well as the study of the role of fecal shedding will involve collection of blood (5 milliliters; 1 teaspoon) and stool (faeces) samples at admission and discharge as well as 2 days, 5 days, 1 month, 2 months, 3 months, 4 months, 5 months and 6 months after admission. Participants will provide consent for clinical follow-up as well as collection of blood and stool samples.
- **Surveillance for active and past SARS-CoV-2 infection.**

- HCW and other non-healthcare frontline workers will provide a nasopharyngeal and oropharyngeal (NP/OP) sample and a 5 milliliter (1 teaspoon) blood sample. Each HCW will provide samples at up to four separate timepoints over one year while each non-healthcare frontline worker will provide up to three samples over 6 months. NP/OP samples will be tested for active SARS-CoV-2 infection and blood samples will be tested to determine if workers had SARS-CoV-2 infection in the past. Additional NP/OP and/or blood samples will not be collected if routinely collected for public health surveillance among specific frontline workers, e.g., truck drivers. Clinical and demographic data will be collected from participants. Consent will not be sought for routine testing directed by Ministry of Health, e.g., among truck drivers. Consent will be sought from participants for research testing.

- **Surveillance for past SARS-CoV-2 infection.**
  - HDSS residents: A single blood sample – 5 milliliters (1 teaspoon) – will be collected. In a small sub-population (10% of the participants), we will collect about 100µL of blood spots (two-hundreths of a teaspoon) using fingerpricks. Clinical and demographic data will be collected from participants. Consent will be sought from participants.
  - Asymptomatic and symptomatic SARS-CoV-2 infected individuals: Blood samples will be collected at 2 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 6 months, 9 months and 12 months after diagnosis (8 samples total over one year). At each sampling point, 5 milliliters (1 teaspoon) for adults and 2 milliliters (less than half a teaspoon) for children below the age 5 years will be collected. Clinical and demographic data will be collected from participants. Consent will be sought from participants.
- **Understanding the effect on hospitals of COVID-19**
  - Hospital managers, senior and junior clinicians (doctors, nurses, pharamcists) will be asked to share their experiences as part of interviews or small group discussions that may be held online or face to face in hospitals during site visits as these become possible

What are the benefits and risks/costs of the study for those involved?

For study questions that will not enroll individuals directly, no costs will be incurred and there are no individual benefits. COVID-19 patients enrolled in the clinical surveillance with 6 months follow-up will need to attend visits at the health facility after discharge and will be reimbursed to offset transport costs (depending on distance traveled) and KES 350 to KES 650 for out-of-pocket expenses. Individuals enrolled in serosurveillance among HDSS residents will be asked to attend one visit at a health facility and will have transport costs reimbursed as well as KES 350 to 650 reimbursement for out-of-pocket expenses. Individuals enrolled in the serosurveillance study among healthcare workers will have transport costs reimbursed and be provided with KES 650 for out-of-pocket expenses if they have been transferred and are asked to attend to their health facility of enrollment for sample collection, or are asked to attend a study visit during their non-working hours. Individuals enrolled in other surveillance studies of active and past SARS-CoV-2 infection will have samples collected at their (participant's) physical location and therefore will not incur study-associated travel costs. No additional tests will be carried out. Follow up home visits will be integrated within the County COVID-19 Rapid Response Team home-based care program and patient follow up. Participants will receive reimbursement for transport and out-of-pocket expenses for any follow up visits to the health facility.

Individuals recruited into clinical surveillance will benefit from tests to guide treatment and close follow up from the research teams. Costs related to study procedures, including research clinical tests, will be fully met by the research team. Individuals will be asked to give their permission before they share any of their experiences and all information they provide will be kept confidential. The aim is to focus on general issues that emerge across multiple facilities so no individual or specific facility will be named in any report. Those being interviewed online will be reimbursed data costs in line with existing KEMRI-Wellcome policies. For a 30-60 minute meeting / interview we provide 1GB of data (cost to KEMRI-Wellcome approximately 250/= KES). Those being interviewed at their place of work are not expected to incur any participant costs.

How will the study benefit society?

The proposed work is expected to provide information that will improve the government's planning in response to COVID-19 and care of COVID-19 patients and help them optimize future hospital services. We therefore expect that some of the findings may improve the health and livelihoods of those living in Kenya and may find use in other countries. The proposed work may also provide information that can help identify additional important topics for future COVID-19 research.

If blood spots are shown to be acceptable, valid and easier to do in the sub-population, they may be adopted for large scale sero-surveillance projects by the Ministry of Health to improve the health of individuals living in Kenya.

When does the study start and finish?

We plan to begin surveillance work related to the national public health response from July 2020 and will continue to provide data that are prioritised by the Ministry of Health and counties for the duration of the pandemic and possibly beyond, depending on the requirements of the Ministry, counties and health facilities involved. Research activities will start upon approval of ethical approval and are expected to continue for one year in the first instance.

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3 List of acronyms and abbreviations

ANC	Antenatal care
BMI	Body Mass Index
CBC	Complete blood count
CHAIN	Childhood Acute Illness and Nutrition Network
CIF	Case Investigation Form
CIN	Clinical Information Network
COVID-19	Coronavirus disease 2019
CPAP	Continuous Positive Airway Pressure
CRF	Case Record Form
CRP	C-reactive protein
eCoV	endemic coronavirus
EOC	Emergency Operations Centre
eQTL	Expression quantitative locus
ESR	Erythrocyte sedimentation rate
GWAS	Genome-wide association studies
HCW	Healthcare worker
HDSS	Health and Demographic Surveillance System
HIV	Human Immunodeficiency Virus
JOOTRH	Jaramogi Oginga Odinga Teaching and Referral Hospital
KCH	Kilifi County Hospital
KEMRI	Kenya Medical Research Programme
KNH	Kenyatta National Hospital
KWTRP	KEMRI-Wellcome Trust Research Programme
LMIC	Low- and Middle-Income Country
MERS-CoV	Middle East Respiratory Syndrome coronavirus
MOH	Ministry of Health
OPD	Outpatient Department
PPE	Personal protective equipment
RRT	Rapid Response Team
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sSA	sub-Saharan Africa
UTM	Universal Transport Medium
VTM	Viral Transport Medium
WHO	World Health Organization

4 Abstract

With more than 10 million confirmed SARS-CoV-2 infections, 500,000 deaths reported by 1st July 2020 and enormous costs to the global economy, the coronavirus disease 2019 (COVID-19) pandemic ranks among the most urgent crises in recent history. While high-income countries appear to be approaching their first epidemic peak, most Low- and Middle-Income Countries (LMICs) are anticipating an exponential increase in cases. In Kenya, over 6,000 cases have been confirmed among more than 170,000 individuals tested and close to 150 deaths reported as of 1st July 2020. The national COVID-19 response is led by the National Emergency Response Committee overseeing the Emergency Operation Centre (EOC). EOC coordinates technical activities at national level and with counties through Rapid Response Teams implementing case identification, contact tracing and isolation.

RT-PCR assays from nasopharyngeal (NP) and oropharyngeal (OP) samples remain the molecular test of choice for the aetiologic diagnosis of SARS-CoV-2 infection currently taking place at six laboratories across the country (including KEMRI Centre for Geographic Medicine, Coast). The sudden increase in demand for nasopharyngeal swabs and viral transport medium generated by the pandemic has exerted pressure on global supply chains for these supplies and hampered mass testing in the country.

The government has instituted measures to slow the progression of the pandemic in Kenya, including promotion of hand hygiene, cough etiquette, and wearing of face masks in public areas, limiting social gatherings, suspension of international passenger flights into and out of Kenya, extended school and workplace closures, introducing a nationwide curfew, restricting travel into and out of “hotspot” counties, and mandatory quarantine for suspected cases. These interventions are aimed at “flattening the epidemic curve” to avert deaths arising from a surge in demand for services exceeding the capacity of the health system. However, these measures are also associated with substantial economic and societal costs. Governments are therefore faced with the dilemma of choosing between minimizing deaths arising directly from COVID-19 and the negative secondary impact of the mitigation measures. The optimal solution to this dilemma relies on the availability of accurate and timely surveillance data to inform planning while strengthening health service delivery.

KEMRI-CGMR-C has a longstanding partnership with the Ministry of Health providing technical support through research, policy engagement and capacity building through its four scientific departments, including well-established high quality clinical surveillance across various health facilities participating in the Clinical Investigation Network (CIN), the Childhood Acute Illness and Nutrition Network (CHAIN) and at the Kilifi County Hospital. This protocol describes a series of clinical and seroepidemiological surveillance and research activities aimed primarily at providing evidence to support the national COVID-19 response in Kenya. Specifically, we aim to (i) undertake surveillance to describe the clinical, demographic, and genomic profile, trends, clinical course and

outcomes of patients with acute respiratory illness including COVID-19 and including post-COVID-19 multisystem inflammatory syndrome, (ii) use serological assays to estimate the seroprevalence of SARS-CoV-2 antibodies among target populations in Kenya, (iii) to determine the quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2 in settings where risk of faecal-oral contamination is high (iv) examine the availability and utilization of resources and organization of health services for the management of COVID-19 and (v) describe the secondary effects of COVID-19 on essential routine health services.

The surveillance work, surveys and interviews proposed here will provide complementary data on COVID-19 in the Kenyan population, organization of available resources for clinical management, and how these change over time to refine existing models of the projected course of the epidemic. The findings will ultimately inform contextualised recommendations on where, among whom, and when existing control strategies should be modified and to inform planning for the possible escalation of the epidemic in Kenya.

5 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus of zoonotic origin, capable of causing a potentially fatal pneumonia-like illness, coronavirus disease 2019 (COVID-19). SARS-CoV-2 is the seventh known coronavirus to infect humans. The other six coronaviruses include four endemic viruses that cause predominantly mild respiratory illness (229E, HKU1, NL63 and OC43) and two zoonoses – SARS coronavirus (SARS-CoV), which caused a global outbreak of severe respiratory disease in 2003, and Middle East Respiratory Syndrome coronavirus (MERS-CoV), which has caused localized outbreaks of severe respiratory illness since 2012 (1). SARS-CoV-2 was first reported in China in December 2019 and spread rapidly thereafter, prompting the World Health Organization (WHO) to declare COVID-19 a pandemic in March 2020 (2). By 1st July 2020, there were more than 10 million confirmed SARS-CoV-2 infections and 500,000 deaths globally. Most confirmed cases as of 1st July 2020 were reported in the US (2.6 million), Brazil (1.4 million) and Russia (647,849) while most deaths were reported in the US (127,410), the UK (43,730) and Brazil (59,594). There were approximately 405,000 and 10,000 confirmed COVID-19 cases and deaths, respectively, in Africa by 1st July 2020. Kenya reported its first case of COVID-19 on 13th March 2020 and by 1st July there were 6,673 confirmed cases among 173,355 individuals tested. In this dynamic situation, data on the number of confirmed SARS-CoV-2 infections and COVID-19 deaths are updated daily (3-5).

5.1 Clinical epidemiology

SARS-CoV-2 has been shown to be transmitted through close contact with infected persons, droplets and through fomites. Airborne transmission – for example during the conduct of medical procedures – is a theoretical route of SARS-CoV-2 infection, but has not been conclusively demonstrated. SARS-CoV-2 has been isolated from faecal samples in a limited number of cases, suggesting potential faecal-oral transmission; no case of faecal-oral transmission has been documented to date (6, 7). The duration from infection to transmission has been estimated to be approximately five days and the reproductive number (average number of susceptible individuals infected by a single infected individual) has been estimated at 2.0 using data from China and 1.8-3.5 in Kenya (8, 9).

Infection with SARS-CoV-2 can be asymptomatic or cause illness ranging from mild respiratory symptoms to severe pneumonia and septic shock. Little is known about the true number of infected persons, the proportion that is asymptomatic, and the distribution of disease severity. Availability of data on these crucial parameters is hampered by limited capacity for virological and serological testing with acceptable specificity and sensitivity, variations in populations targeted for testing globally, as well as variations in healthcare-seeking practices and access to healthcare globally and at the sub-national level. For example, testing of asymptomatic close contacts is performed in Kenya, but is not routinely recommended in South Africa (10). In addition, disease transmission in the asymptomatically infected may be common. For example, on the Diamond Princess cruise ship epidemic of 634 passengers and crew who tested positive for SARS-CoV-2, 328 (52%) did not have any symptoms (11). Based on a study

of approximately 45,000 confirmed, symptomatic, predominantly adult (98%) COVID-19 cases in China, the distribution of mild/moderate, severe and critical disease was 81%, 14% and 5%, respectively, with death occurring in 50% of critically ill patients who also accounted for all deaths in the cohort. In Kenya, 2.093 cases had been confirmed as of 2nd June 2020. Of the total positive (confirmed) cases, 1,777 (85%) reported no symptoms at the time of initial testing (12).

Data from non-African populations indicate that progression to severe disease occurs in the second week after onset of disease (13, 14). Progression to severe COVID-19 has been associated with age >60 years, pre-existing comorbidities as a composite and hypertension, cardiovascular disease and chronic respiratory disease, specifically (15). Risk factors for COVID-19 death are largely similar with a suggestion of increased risk of death for individuals aged >68 years and increased risk of death in individuals with hypertension, cardiovascular disease, cerebrovascular disease, chronic respiratory disease, malignancy and diabetes (14, 16-18). Available data suggest that SARS-CoV-2 infection causes severe illness less frequently in children and adolescents compared to adults.

Emerging reports indicate a newly-identified syndrome of severe multisystem inflammation, rash and cardiac dysfunction occurring about one month after COVID-19 exposure or infection among children and adolescents. Clinical features of this syndrome include rash, conjunctivitis, muco-cutaneous inflammation, hypotension, shock, myocardial dysfunction, coagulopathy and gastrointestinal problems (diarrhoea, vomiting, or abdominal pain). The precise pathophysiology, clinical course and long-term outcome of this novel syndrome are currently unknown and will require detailed surveillance and follow up to develop understanding. This syndrome has been highlighted as a priority by the WHO (19, 20).

There is currently no approved treatment for COVID-19. Several global research trials are underway to identify drugs and vaccines for treatment and prevention of COVID-19. Drugs under study include hydroxychloroquine/ chloroquine, remdesivir and lopinavir/ ritonavir while at least 10 inactivated, protein sub-unit and DNA candidate vaccines are under clinical study and more than 100 vaccine candidates in pre-clinical studies (21-23).

Evidence on the clinical course of disease and risk factors has largely been drawn from studies in China (15, 24) and there are currently no data from sub-Saharan Africa (sSA). Whether the mechanistic underpinnings of adverse outcomes vary by risk factor remains unknown. A substantial proportion of individuals in sSA are predisposed to pulmonary-associated risk factors that are virtually non-existent in high income countries. For example, previous work has shown that the extensive use of biomass-based fuels at the household level is driving a generally unnoticed epidemic of chronic lung disease in sSA, including chronic obstructive pulmonary disease whose onset age in sSA is 20-30 years earlier than in high-income settings (25, 26). In addition, other risk groups, including undernourished children and human immunodeficiency virus (HIV)

infected populations – who are significantly more likely to die from more traditional pneumonia etiologies (27, 28) – may be especially at risk of death from SARS-CoV-2.

Micronutrient deficiencies, such as iron and vitamin D deficiency, may also influence susceptibility and clinical outcome of COVID-19 infection. Studies suggest that dysregulation of iron status is a hallmark of COVID -19 infection. In Chinese and European patients respiratory failure and death were associated with reduced haemoglobin and iron levels and higher ferritin levels (14, 29). Iron deficiency impairs host immunity and is associated with susceptibility to respiratory tract infections (30). A recent systematic review and meta-analysis including 189 observational studies and 57,563 COVID-19 patients indicated that low haemoglobin and high ferritin levels are strong predictors of disease severity and reduced survival (31). It is thought that vitamin D status might explain variation in the incidence of clinical infection and the severity of COVID-19 infection (32). Vitamin D enhances cellular innate immunity, which can lower viral replication rates (33) and vitamin D supplementation protects from acute respiratory infections (34). Emerging literature indicates that COVID patients are more likely to be vitamin D deficient (35). A small randomized controlled trial (n=76) indicated that adjunctive vitamin D supplementation to COVID-19 patients reduced the need for ICU treatment and possibly mortality (36). There is no information on how iron and vitamin D deficiency might influence COVID-19 infection in Africa.

5.2 Sero-epidemiology

SARS–CoV-2 serological tests using clinical samples (e.g. blood or saliva), such as enzyme-linked immunosorbent assays or lateral flow assays, have the potential to detect SARS-CoV-2 infection beyond the acute phase and to provide rapid results in a wide range of settings. However, their diagnostic utility is thought to be limited early on in the disease before antibody responses have developed (37). Studies in COVID-19 patients from China (Hong Kong, Chongqing, Shenzhen) and Europe (France, Germany) with a cumulative sample of 500 patients provide some limited heterogeneous information(38-41) on SARS-CoV-2 antibody kinetics. In these studies, anti-SARS-CoV-2 IgA, IgG and IgM responses were evaluated using ELISAs targeting either the entire SARS-CoV-2 spike (S) protein, receptor binding domain (RBD) of the S protein or nucleoprotein (NP). Seroconversion rates ranged from 65% (anti-RBD IgG) to 100% (anti-spike, anti-RBD or anti-NP IgA, IgG and IgM). Time to median seroconversion ranged from 6-22 days post-symptom onset. While one study found that antibody levels were not correlated with disease severity,(40) others found that high IgG levels were associated with disease severity.(38, 41) One study found that IgG and IgM levels were not associated with chronological age.(40) There was heterogeneity in the sequence of IgM vs. IgG antibody responses, with IgM detected first in some individuals,(38, 41) IgG first in others(38, 40) and simultaneous detection of IgM and IgG in others.(38) One study found that antibody levels were positively correlated with viral neutralization titers(40) and another suggested waning in IgG titers three weeks post-symptom onset.(38) The longest observation period in these studies was 39 days post-symptom onset, therefore, there is no information available on long-term antibody

kinetics and the duration of immunity induced by SARS-CoV-2 infection remains unknown.

Emerging estimates of population-level exposure to SARS-CoV-2 range from 0% among adult patients in a region of Finland and blood donors in a region of France to 36% among contacts of a case at a high school in France (42). In Kenya, serosurveillance among blood donors – a presumed healthy population – indicated 5% seroprevalence by June 2020 (43). In some other settings, 5% seroprevalence has been observed after communities have gone through a pandemic wave. The blood donor seroprevalence data therefore suggest that Kenya was in an advanced stage of the pandemic locally by June 2020. Seroprevalence estimates will vary by epidemic phase, geographical distribution of the local epidemic and population included in serosurveillance, as can be seen in available seroprevalence data. The development of validated serologic (antibody) assays that assess prior infection and immunity to SARS–CoV-2 will be essential for epidemiologic studies to estimate attack rates or case-fatality rates, population surveillance, vaccine trials, and policy decision making to strategically deploy immune frontline staff and to inform the release of control measures (44). Immunoassays are already on the market in some countries, however their diagnostic accuracy (sensitivity and specificity – using RT-PCR as the gold standard – in the presence of other circulating human coronaviruses) and clinical utility in defining immunity from subsequent reinfection remain undefined.

Reliable serological assays with high throughput are essential for undertaking rapid surveys to determine the proportion of individuals in the general population or in high-risk groups exposed to SARS-CoV-2. An increasing number of commercial assays are now available to support this need. However, the performance of these assays will need to be validated locally among confirmed cases and pre-pandemic specimens before deployment at scale.

The SARS-CoV-2 pandemic exposed a need for high quality disease sero-surveillance at a population level. Frequently, cost and lack of skilled manpower have impeded population-level based sero-surveillance programs. It is important to assess for technology that makes micro sampling (such as the use of dried blood spots [DBS]) both logistically feasible to implement and acceptable to the general population

5.3 Host genetics

The host genetic factors determining inter-individual variation in COVID-19 severity are not well understood. Previous studies on the human genetic basis of infectious disease have identified mutations in genes that result in resistance or susceptibility to severe diseases such as malaria caused by Plasmodium vivax (*DARC*) (45), severe pneumonitis caused by influenza virus or rhinovirus (*IRF7*, *IRF9*, *TLR3*, *IFIH1*) (46-50), encephalitis caused by herpes simplex virus (*TLR3*, *TRAF3*, *IRF3*) (51-53), and HIV (*CCR5*) (54-56).

Variants in the human angiotensin converting enzyme 2 (*ACE2*) gene that encodes the host cell surface receptor for SARS coronaviruses, were identified in the previous

SARS-CoV outbreak, and these variants play an important role in the binding of the viral spike protein (57). More studies are needed to determine whether these variants modulate the current SARS-CoV-2 binding to the ACE2 receptor, and whether they might influence COVID-19 severity. More recent target gene studies have implicated variants in other genes with COVID-19 severity, including *ApoE* e4 genotype in a population from the United Kingdom (58), and the *ABO* locus in Chinese and American populations (59, 60).

Hypothesis-free genome-wide association studies (GWAS) are also being carried out, with the latest study in individuals from Italy and Spain also implicating the ABO locus, with higher risk of infection for blood group A and a protective effect for blood group O (61). This GWAS has also identified a variant in a gene cluster that includes the *SLC6A20* gene, which encodes the sodium/imino-acid (proline) transporter 1 (SIT1), an ACE2 interacting partner (62, 63). This cluster also contains chemokine receptor genes such as *CCR9* and *CXCR6*, which play an important immunomodulatory role in influenza viral infections (64). Preliminary findings from a genome-wide association study in the United Kingdom utilizing UK Biobank samples has identified a variant in the *XPNPEP2* gene in the X chromosome that confers a protective effect against infection (65). Preliminary findings from a genome-wide association study in the United Kingdom utilizing UK Biobank samples has identified a variant in the *XPNPEP2* gene in the X chromosome that confers a protective effect against infection[21]. This gene encodes the protein aminopeptidase P, which degrades bradykinin, a potent vasodilator peptide that is also degraded by ACE2 (66, 67). Of note from this study is that the signal in *XPNPEP2* was only significant in white European ancestry individuals only, and not in other ancestries. This underscores the importance of carrying out more host genetics studies in diverse populations, to further understand the nature of disease risk in different populations. Furthermore, combining genotype and gene-expression data using expression quantitative locus (eQTL) mapping approaches could further elucidate the functional effects of genetic variants in both coding and non-coding regions that are associated with COVID-19 severity.

5.4 COVID-19 and health services

To minimize the risk of transmitting the virus to either patients or health care workers, health facilities have decongested their clinical areas by reducing staff levels, and deferring elective and routine visits. Care-seeking behaviour may also be adversely affected by patients avoiding visits out of fear of exposure to infection. A surge in cases is anticipated to result in diversion of staff and resources from key service areas to the management of COVID-19 patients. The situation may be worsened further by absenteeism as a result of infection of hospital staff. Analyses from the previous Ebola outbreaks in West Africa suggest that preventable deaths caused by measles, malaria, tuberculosis and HIV, and attributable to failures of the health system exceeded deaths from Ebola (68-70). Secondary effects of COVID-19 on the health system require active monitoring and reporting, particularly in low resource settings to ensure continuity of essential services that are already overstretched.

5.5 Kenya National COVID-19 response

The COVID-19 response in Kenya is coordinated by the National Emergency Response Committee, which oversees technical functions of the Emergency Operation Centre (EOC). Counties coordinate sub-national Rapid Response Teams (RRT) that report to the EOC. The COVID-19 response in Kenya has focused on early case identification, contact tracing and isolation. Physical distancing and hand hygiene have been promoted by the Ministry of Health as preventive measures. To promote physical distancing, the government has encouraged work-from-home, suspended large gatherings inclusive of school closures, and overnight curfews have been implemented nationally. In contexts where physical distancing may be challenging to implement, such as in supermarkets and on public transport, use of face masks is required. As containment measures, limited lockdowns have been implemented in the Nairobi metropolitan area (which has the largest number of cases), Kilifi, Kwale, Mombasa and Mandera Counties, and international commercial travel has been halted with a view of flattening the epidemic curve.

KEMRI's Centre for Geographic Medicine, Coast has a longstanding partnership with the Ministry of Health providing technical support through research, policy engagement and capacity building through its four scientific departments, including well-established high quality clinical surveillance across various health facilities participating in the Clinical Investigation Network (CIN), the Childhood Acute Illness and Nutrition Network (CHAIN) and at the Kilifi County Hospital. KEMRI-Wellcome Trust Research Programme (KWTRP) Kilifi laboratories are the designated COVID-19 testing centre for the Coast region. Additional engagement from KWTRP in the COVID-19 response includes: (i) epidemiological and health system modelling, (ii) development and implementation of COVID-19 case management guidelines (iii) evidence synthesis on effectiveness of available interventions and approaches to epidemic control (iv) direct support for sentinel surveillance, analytics and reporting systems for EOC, and (v) technical support to the Kilifi County RRT.

This protocol describes the range of existing and planned surveillance activities contributing to the national COVID-19 response.

6 Justification for the study

This study will generate local data – such as the proportion of exposed individuals, those who become symptomatic, the distribution of disease severity among symptomatic cases, clinical course of disease and disease transmission patterns in Kenya – which can inform COVID-19 models but are currently not available. Modelling is an essential tool for forecasting the COVID-19 epidemic in Kenya and exploring the effect of varying levels of control measures on the epidemic..

The clinical course of disease in Kenyan patients has not been well-described and the impact of locally relevant vulnerabilities such as malnutrition and HIV-infection on the clinical course of disease is unknown. Beyond input into disease models, understanding groups at increased risk of COVID-19 can help develop targeted disease control and

prevention measures at the national and sub-national level. Furthermore, locally-relevant host genetic factors determining inter-individual variation in COVID-19 severity and disease molecular mechanisms in locally-relevant vulnerable groups - which could inform locally-appropriate therapeutics – are unknown.

Symptomatic testing for viral infection will miss exposed asymptomatic individuals and mass testing for viral infection will miss previously exposed individuals and may generate non-representative data if not conducted using a specified methodological approach. Furthermore, symptomatic and mass testing are limited by availability of consumables, reagents and personal protective equipment (PPE). Serological studies can provide insights into the extent of exposure to SARS-CoV-2 in populations, i.e., they can inform estimates of the population that may have been exposed to SARS-CoV-2 and mounted an immune response. In the local context, serological studies in various populations, collectively, can inform modifications to COVID-19 control measures. Throughout the course of the pandemic, contact with healthy representatives of the population will continue in antenatal care (ANC) clinics. In these settings, blood is routinely drawn for infection screening. Residual samples from ANC clients may be used to test for SARS-CoV-2 antibodies. While these data cannot be directly generalised to the population, the approach may provide rapid insights for urgent policy decision-making. Seroprevalence studies in more representative populations, such as HDSS residents, may be more logistically challenging to conduct given restrictions associated with COVID-19 control measures, but nevertheless will be important to inform pre- and/or post-epidemic population exposure to SARS-CoV-2. Furthermore, understanding the potency with which immunity is stimulated and longevity of the response across the spectrum of cases, including asymptomatic, PCR-confirmed SARS-CoV-2 cases, and symptomatic acute and convalescent patients may provide an indication of the extent of herd immunity thus informing decisions on how to limit the collateral effects of COVID-19 on health, the economy and society.

At the same time, key frontline staff, such as healthcare workers (HCW) are at high risk of infection with SARS-CoV-2. For example, reports from HCWs unions indicate that 20 (9%) of the 216 confirmed SARS-CoV-2 infected cases in Kenya as of 14th April 2020 were HCW (nurses, doctors, clinical officers). Apart from worsening the already severely constrained pool of HCW available to deal with the pandemic, these HCW are at risk of transmitting the infection to patients under their care. Knowledge of the extent of infection among HCW is needed in order to guide decision-making on infection prevention and control measures in health facilities and in the community. Understanding the extent of SARS-CoV-2 exposure in workers serving in other key, front-facing, service areas such as port workers and truck drivers will be important for informing when and how to ease COVID-19 control measures for critical services.

It will be important to validate seroprevalence estimates generated from local SARS-CoV-2 serosurveys, such as the Kenya blood donor seroprevalence survey (43). One way to interrogate such data could be through retrospective serosurveys using samples collected in the periods before and after COVID-19 was thought to have been

introduced in Kenya. Anti-SARS-CoV-2 IgG seropositivity among blood donors in Kenya (43) may be explained by a few cases of COVID-19 infections in late February (71), before confirmation of the first COVID-19 case in the country on March 12, 2020. Should retrospective surveys suggest development of SARS-CoV-2 antibodies before March 2020, additional investigations would be needed to inform whether these results indicate true SARS-CoV-2 infection or whether any positive results are due to assay cross-reactivity with endemic coronavirus (eCoVs)..

While establishing capacity to respond to increased cases of COVID-19, counties must maintain delivery of essential health services, especially those that serve women and children, who are particularly vulnerable during emergency situations. To ensure this is achieved, there is need to conduct regular audits of quality of care and organization of health services against the national standards, to examine the challenges faced in providing new and existing services and provide periodic reports to counties and MOH to guide action.

KWTRP is collaborating with partners in response to a formal request from the Ministry of Health to support COVID-19 surveillance activities to inform policy decision making. This study will generate context-specific evidence to guide the national and sub-national response to COVID-19 in Kenya and inform regional and global strategies for pandemic control.

There is a need to leverage technology to make micro-sampling both easier to do(logistically feasible) and more acceptable to general population. This study will pilot a micro-sampling technique (the Mitra cartridge device) (72) that could make the collection of population-level sero-surveillance samples easier, more acceptable and ensure sample integrity.

7 Null hypothesis

A null hypothesis is not appropriate; these are a series of activities to describe the epidemiology of SARS-CoV-2 infection.

8 Objectives

8.1 Overall aim

To evaluate the demographic and clinical characteristics, effects on health service, seroepidemiology, genomic and molecular mechanisms of COVID-19 in Kenya so as to inform national and county-level response to the COVID-19 pandemic and locally relevant scientific understanding of SARS-CoV-2 infection.

8.2 Primary objective

To estimate the burden of COVID-19 and prevalence of exposure to SARS-CoV-2 among targeted populations in Kenya.

Incidence of suspected[2] or confirmed[3] COVID-19 will be described in hospitalized children and adults. Cumulative incidence[4] of SARS-CoV-2 infection will be estimated in healthcare workers (HCW) and non-healthcare frontline workers. In all cases, clinical and demographic characteristics of infected individuals – including the proportion who are asymptomatic – will be described. Prevalence of exposure to SARS-CoV-2[5] – including age-sex specific prevalence of SARS-CoV-2 IgG/IgM and trends in seroprevalence over time – will be estimated in antenatal clinic (ANC) clients, HCW, non-healthcare frontline staff, asymptomatic[6] individuals, pre-symptomatic[7] individuals, symptomatic[8] (acute and convalescent) individuals, hospitalized non-COVID children and adults, and demographic surveillance residents (except for trends in seroprevalence).

Table 1: Summary of primary objective

Target population	Epidemiologic measure
Hospitalized children and adults	• Incidence of suspected or confirmed COVID-19 • Age-sex specific seroprevalence of SARS-CoV-2 IgG/IgM • Trends in seroprevalence of SARS-CoV-2 IgG/IgM over time
Healthcare workers	• Cumulative incidence of SARS-CoV-2 infection • Age-sex specific prevalence of SARS-CoV-2 IgG/IgM • Trends in seroprevalence of SARS-CoV-2 IgG/IgM over time
Non-healthcare frontline staff and	• Cumulative incidence of SARS-CoV-2 infection

[2] **Suspected COVID-19 Definition 1**: A patient with acute respiratory illness (fever or cough or shortness of breath), AND a history of travel to a foreign country during the 14 days prior to symptom onset; OR having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset.
Suspected COVID-19 Definition 2: A patient with severe acute respiratory illness (fever or cough or shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation (Kenya Ministry of Health. Case definition for novel coronavirus disease (COVID-19) – V25032020. Available from: http://www.health.go.ke/wp-content/uploads/2020/04/COVID-19-Case-Definition-25-March-2020.pdf. Accessed 19 April 2020)

[3] **Confirmed COVID-19:** A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms (Kenya Ministry of Health. Case definition for novel coronavirus disease (COVID-19) – V25032020. Available from: http://www.health.go.ke/wp-content/uploads/2020/04/COVID-19-Case-Definition-25-March-2020.pdf. Accessed 19 April 2020)

[4] **Cumulative incidence of SARS-CoV-2 infection:** Number of new cases of COVID-19 as diagnosed by RT-PCR divided by all individuals at the start of the observation period

[5] **Prevalence of SARS-CoV-2 exposure (seroprevalence)**: Number of individuals with SARS-CoV-2 antibodies divided by all individuals tested for SARS-CoV-2 antibodies

[6] **Asymptomatic**: Individuals with no signs or symptoms of acute illness

[7] **Pre-symptomatic**: Individuals with no signs or symptoms or acute illness at the time of COVID-19 diagnosis, but who develop signs or symptoms of acute illness post-diagnosis

[8] **Symptomatic**: Individuals with signs or symptoms associated with acute illness, not limited to those commonly associated with COVID-19 such as cough, fever and difficulty breathing.

	• Age-sex specific prevalence of SARS-CoV-2 IgG/IgM • Trends in seroprevalence of SARS-CoV-2 IgG/IgM over time
ANC clients	• Age-specific prevalence of SARS-CoV-2 IgG/IgM • Trends in seroprevalence of SARS-CoV-2 IgG/IgM over time
Demographic surveillance system residents	• Age-specific prevalence of SARS-CoV-2 IgG/IgM
Asymptomatic, pre-symptomatic SARS-CoV-2-infected individuals	• Age-specific prevalence of SARS-CoV-2 IgG/IgM • Trends in seroprevalence of SARS-CoV-2 IgG/IgM over time
Symptomatic (acute and convalescent) SARS-CoV-2-infected individuals	• Age-specific prevalence of SARS-CoV-2 IgG/IgM • Trends in seroprevalence of SARS-CoV-2 IgG/IgM over time

8.3 Specific secondary objectives

1. To describe the clinical presentation, course and outcomes and determine the quantity, duration and contribution to transmission of viable faecal shedding of SARS-CoV-2 in hospitalized COVID-19 patients.

   The clinical presentation, course and outcomes of COVID-19, including risk factors, will be described in all hospitalized cases as well as in more detail among highly vulnerable adults (such as those with HIV and chronic non-communicable diseases) and highly vulnerable children (such as those with malnutrition). We will also investigate whether micronutrient deficiencies, such as iron and vitamin D deficiency are associated with risk and clinical outcome. The description of clinical epidemiology in COVID-19 cases will include evaluation of multisystem inflammatory syndrome in children and adolescents.
2. To describe and compare trends in hospitalization and mortality due to all causes and pneumonia in adults and children.
3. To examine utilization of respiratory care interventions, up-referral, down-referral, criteria for discharge and determine the impact of local SARS-CoV-2 response on the ability of the Kenyan health system to continue to deliver other health services, including management of acute illness (diarrhoea, pneumonia, malaria, HIV), nutritional rehabilitation, follow-up care and prevention of mother to child HIV infection.
4. To investigate host genetic determinants of susceptibility to COVID-19, and molecular mechanisms of SARS-CoV-2 severity and death in hospitalized adults with long-term biomass exposure and severe undernutrition.

Methods: Overview of included studies

The table below summarizes the studies included under this protocol. This table is intended to orient the reader to the various studies included under this protocol and is not intended to be exhaustive. Detailed methods for each study are provided in Sections 9 -13.

Study (design)	Objective	Sites	Population	Sample size	Research samples	Frequency
Clinical surveillance and health services						
Incidence of suspected and confirmed COVID-19 (population surveillance)	Primary objective	CIN/ CHAIN health facilities - Please see Table 2, Kenyatta University Teaching, Referral and Research Hospital	Children and adults	All admitted to study health facilities	None	
Clinical presentation, course and outcome, including risk factors (population surveillance)	Secondary objective #1	CIN/ CHAIN health facilities - Please see Table 2, Kenyatta University Teaching, Referral and Research Hospital	Children and adults	All eligible patients with available data	None	
Clinical surveillance for multisystem inflammatory syndrome (CHAIN-COVID cohort)	Secondary objective #1	CIN/ CHAIN health facilities - Please see Table 2	Individuals <18 years of age with multisystem inflammatory syndrome symptoms	All meeting eligibility criteria	Blood (5mL) NP swab* Faecal Rectal swab	Enrollment; 2 and 5 days post-enrollment; at discharge; and 1, 2, 3, 4, 5, and 6 months post-enrollment

Study (design)	Objective	Sites	Population	Sample size	Research samples	Frequency
Clinical presentation, course and outcomes – including risk factors – in highly vulnerable adults and children (CHAIN-COVID cohort)	Secondary objective #1	CIN/ CHAIN health facilities - Please see Table 2	Children with and without acute malnourishment Adults with and without HIV and other chronic non-communicable conditions	600 children aged <15 years 600 individuals aged ≥15 years	Blood (5mL) NP swab* Faecal Rectal swab	Enrollment; 2 and 5 days post-enrollment; at discharge; and 1, 2, 3, 4, 5, and 6 months post-enrollment
Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2 (CHAIN-COVID cohort)	Secondary objective #1	CIN/ CHAIN health facilities - Please see Table 2	Samples from CHAIN-COVID cohort	200 samples (100 positive by RT-PCR at enrollment and Day 30)	None – will use faecal and rectal swab samples from CHAIN-COVID cohort	N/A
Trends in hospitalization and mortality due to all causes and pneumonia in adults (population surveillance)	Secondary objective #2	Kilifi County Hospital (KCH)	Patients admitted to the KCH adult wards	All admitted patients	None	
Qualitative exploration of the challenges facilities face in providing COVID-19 and routine services	Secondary objective #3	CIN/ CHAIN health facilities - Please see Table 2 and COVID specific facilities	Senior and junior health workers who manage/lead services or provide care	Between 20-30 interviews and 4-6 small group discussions (until the point no major new findings emerge)	None	N/A

Study (design)	Objective	Sites	Population	Sample size	Research samples	Frequency
Micronutrient studies	Secondary objective #1	KCH, KNH, CGTRH, Mbagathi hospital, JOOTRH, Nairobi County, Mombasa County and Uasin Gishu County	Samples from: - Asymptomatic serosurveillance cohort - COVID-19 cases at KCH - HCW serosurveillance cohort	All admitted symptomatic patients, 150 asymptomatic cases and 300 HCW	None – residual blood (300µl) will be used	N/A
Virological and serological surveillance						
Virological and serological surveillance (longitudinal study)	Primary objective	- KCH - Kenyatta National Hospital (KNH) - Coast General Teaching and Referral Hospital (CGTRH) - Mbagathi County Hospital - Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) - Aga Khan University Hospital	HCW	4500	NP/OP swab Blood (5mL)	Enrollment, 4, 8 and 12 months post-enrollment

Study (design)	Objective	Sites	Population	Sample size	Research samples	Frequency
Virological and serological surveillance (longitudinal study)	Primary objective	Up to three organizations sectors among: - Truckers - Kenya Ports Authority (KPA) - Kenya Airports Authority (KAA) - Kenya Airways	Non-healthcare frontline workers	2100	NP/OP swab Blood (5mL)	Enrollment, 3 months and 6 months post-enrollment
Serological surveillance (repeated cross-sectional survey)	Primary objective	- KCH - KNH - CGTRH - Mbagathi County Hospital - JOOTRH	Antenatal clinic (ANC) clients	8100	None – will use residual blood from samples collected at ANC appointments	N/A
Serological surveillance (cross-sectional survey)	Primary objective	Kilifi Health and Demographic Surveillance System (HDSS) Nairobi HDSS Manyatta HDSS	HDSS residents (adults and children)	2550	Blood (5mL)	Once (at enrollment)
Serological surveillance (longitudinal study)	Primary objective	- Nairobi County - Mombasa County - Uasin Gishu County	Asymptomatic PCR-confirmed SARS-CoV-2 infected adults and children	200	Blood (2mL for children aged <5 years; 5mL for individuals aged ≥5 years)	2 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 6 months, 9 months and 12 months post-enrollment

Study (design)	Objective	Sites	Population	Sample size	Research samples	Frequency
Serological surveillance (longitudinal study)	Primary objective	- Aga Khan University Hospital - KNH - Kenyatta University Teaching Research and Referral Hospital - Moi University Teaching and Referral Hospital	Symptomatic PCR-confirmed SARS-CoV-2 infected adults and children	All eligible	Blood (2mL for children aged <5 years; 5mL for individuals aged ≥5 years)	2 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 6 months, 9 months and 12 months post-enrollment
Serological survey (retrospective study)	Primary objective	- Kilifi County Hospital	Hospitalized non-COVID children and adults	Approximately 1600 annually	None. Will use stored samples	N/A
Host genetics studies						
Target gene analysis Genome-wide studies	Secondary objective #4	Clinical, virological and serological surveillance sites	SARS-CoV-2 infected and uninfected children and adults	500	None – will use portion of blood samples collected from CHAIN-COVID cohort, serological surveillance studies and other KWTRP studies	N/A
Molecular mechanisms study	Secondary objective #4	Clinical and virological surveillance sites	SARS-CoV-2 infected and uninfected children and adults	500	None – will use residual NP samples collected from clinical and virological surveillance	N/A

9 Clinical surveillance and health services studies

9.1 Linked objectives

9.1.1 Clinical surveillance objectives

- To estimate the burden of COVID-19 (primary objective).
- To describe the clinical presentation, course and outcomes and determine the quantity, duration and contribution to transmission of faecal shedding of viable SARS-CoV-2 in hospitalized COVID-19 patients (secondary objective #1).
- To describe and compare trends in hospitalization and mortality due to all causes and pneumonia in adults and children(secondary objective #2).

9.1.2 Health services assessment objectives

- To examine utilization of respiratory care interventions, up-referral, down-referral, criteria for discharge and determine the impact of local SARS-CoV-2 response on the ability of the Kenyan health system to continue to deliver other health services, including management of acute illness (diarrhoea, pneumonia, malaria, HIV), nutritional rehabilitation, follow-up care, prevention of mother to child HIV infection, and immunization services (specific secondary objective #3)

9.2 Design and methodology – Clinical surveillance and health services studies

9.2.1 Sites

9.2.1.1 Clinical surveillance

Both paediatric and adult clinical surveillance will be conducted at health facilities with ongoing KWTRP clinical surveillance platforms: Clinical Information Network (CIN), Childhood Acute Illness and Nutrition Network (CHAIN) and Kilifi County Hospital. These health facilities may include those listed in Table 1. As such, COVID-19 clinical surveillance and health services studies will leverage ongoing surveillance and research work approved under KEMRI SERU #3459 (Clinical Information Network – A technical collaboration with the Ministry of Health and county hospitals to support and improve strategies for audit and health service evaluation), SSC #1433 (An effectiveness study in Kilifi District of 10-valent Pneumococcal Conjugate Vaccine administered through the routine childhood immunization programme) and SSC#1999 (Description of the profile of disease in adults admitted in Kilifi County Hospital). Additional health facilities will be invited to take part if they are recommended by the Ministry of Health or Counties, have an interest in engaging and there is capacity to include them.

Table 2. COVID-19 clinical surveillance sites

County	Health facility	County	Health facility
Busia	Busia County Referral Hospital	Embu	Embu Level 5 Teaching & Referral Hospital
Bungoma	Bungoma County Referral Hospital	Nakuru	Naivasha County Referral Hospital
Kisumu	Jaramogi Oginga Odinga Teaching		Nakuru Level 5 Hospital

County	Health facility	County	Health facility
	and Referral Hospital		
	Kisumu County Hospital	Nairobi	Mama Lucy Kibaki Hospital
Homa Bay	Homabay County Referral Hospital		Mbagathi County Hospital
			Kenyatta National Hospital
Vihiga	Vihiga County Referral Hospital		Pumwani Maternity Hospital
Kakamega	Kakamega County General Teaching & Referral Hospital	Nyeri	Nyeri County Referral Hospital
Trans-Nzoia	Kitale County Hospital	Kirinyaga	Kerugoya County Referral Hospital
Migori	Migori County Hospital	Kiambu	Kiambu Level 5 Hospital
	Nyatike Sub-County Hospital (Macalder) Hospital		Thika Level 5 Hospital
Machakos	Machakos Level 5 Hospital	Mombasa	Coast General Hospital
Kisii	Kisii County Hospital	Kilifi	Kilifi County Hospital

9.2.1.2 Health services assessment

Health system capacity monitoring will be based on the Ministry of Health's COVID-19 Health Facility Assessment Tools and aligned with the WHO's Hospital Readiness checklist for COVID-19 .

Monitoring will be conducted in health facilities where clinical surveillance will be conducted, which may include those health facilities listed in Table 1.

Interviews or small group discussions will be conducted with senior clinical staff and managers as well as frontline workers (including physicians, clinical officers, nurses and pharmacists where appropriate) to explore the challenges they face in providing COVID-19 specific care or maintaining existing services.

9.2.2 Study population

9.2.2.1 Clinical surveillance

9.2.2.1.1 Surveillance for all suspected or confirmed COVID-19 (primary objective #1 and secondary objective #1)]

We will seek to enrol all paediatric and adult patients including suspected and confirmed COVID-19 hospitalized cases at participating health facilities, defined as neonates, children and adults who meet the Kenyan National suspected or confirmed COVID-19 case definition at presentation to hospital or during an inpatient stay. The Kenya National COVID-19 case definition is subject to change in this rapidly evolving situation. As of March 25, 2020, the following case definition applied:

- "Suspect case:
  - A patient with acute respiratory illness (fever or cough or shortness of breath), AND
    - A history of travel to a foreign country during the 14 days prior to symptom onset; OR
    - Having been in contact with a confirmed or probable COVID-19 case…in the last 14 days prior to symptom onset
  - A patient with severe acute respiratory illness (fever or cough or shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation
- Confirmed case:
  - A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms" (73)

All children and adolescents aged <18 years admitted to hospital will be assessed for SARS-CoV-2-associated multisystem inflammatory syndrome using the case definition below, adapted from the WHO preliminary case definition below and if meeting these criteria, included in our cohort study and followed up for a period of 6 months to better understand health outcomes after discharge from hospital:

Children 0-19 years of age with fever for ~3 days

AND

Two of the following:

a. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
b. Hypotension or shock
c. Features of myocardial dysfunction, pericarditis, valvulitis, coronary abnormalities including ECHO findings or elevated Troponin/ NT-proBNP), or evidence of coagulopathy (PT, PTT, elevated d-Dimers) *OR other evidence of cardiac dysfunction where these tests are not available**
d. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)

AND

Elevated markers of inflammation such as ESR, CRP, or procalcitonin

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes

AND

Evidence of COVID (RT-PCR test or serology positive), or likely contact with patients with COVID

**in italics, modified for surveillance in limited resource settings*

9.2.2.1.2 Sub-group eligibility criteria

9.2.2.1.2.1 Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2 (secondary objective #1)

Criteria for inclusion:

- Planning to remain within the hospital catchment area and willing to come for follow-up visits (monthly visits for 6-months).
- Patient willing to consent, or for children a parent or guardian who consents on a child's behalf (where possible assent will also be sought from children over the age 13)

Criteria for exclusion of all subjects

- Previously enrolled in this study
- Referred from another facility and having been a suspected case for longer than 24 hours.
- Suspected cases who have been at the study hospital for more than 24 hours.

9.2.2.1.2.2 Clinical presentation, course and outcomes – including risk of death in the inpatient and post-discharge periods – in highly vulnerable adults and children (secondary objective #1)

Criteria for inclusion:

- Planning to remain within the hospital catchment area and willing to come for specified follow-up visits
- Patient willing to consent, or for children a parent or guardian who consents on a child's behalf (where possible - e.g. well-enough and with mental capacity to provide assent - assent will also be sought from children over the age 13)
- Children aged 2 months – 15 years of age with WHO defined severe acute malnutrition and children without severe acute malnutrition
- Individuals aged ≥15 years of age with existing diagnoses of chronic lung disease; moderate to severe asthma; heart failure; congenital heart disease;

immunocompromise (HIV, other immune deficiency, or currently taking immunosuppressive drugs including prolonged corticosteroids); diabetes; chronic kidney disease being treated by dialysis, chronic liver disease or severe obesity (BMI ≥40).

Criteria for exclusion of all subjects

- Previously enrolled in this study
- Referred from another facility and having been a suspected case for longer than 24 hours.
- Suspected cases who have been at the study hospital for more than 24 hours.

9.2.2.1.2.3 Micronutrient studies of vitamin D and iron status

- Asymptomatic adults or children with COVID-19 from serosurveillance cohort (See Section 11)
- COVID-19 cases at KCH
- HCW serosurveillance cohort (See section 11)

9.2.2.1.2.4 Trends in hospitalization and mortality due to all causes and pneumonia in adults (secondary objective #2)

- All individuals admitted to KCH adult wards
- Individuals admitted to KCH adult wards with clinical pneumonia. Clinical pneumonia is defined as the presence of any two of the following symptoms within the past 14 days before admission: cough, fever, chest pain, crackles, haemoptysis, dyspnea

9.2.2.2 Health services assessments

These activities will include simple inventories of available resources complemented by interviews and small-group discussion with health care workers who manage or provide services. Inclusion criteria:

- Willing to provide consent
- Hospital managers, senior and junior clinicians (doctors, nurses, pharamcists etc.)

9.2.3 Sampling

9.2.3.1 Clinical surveillance

9.2.3.1.1 Estimation of the burden of COVID-19 (primary objective)

All patients meeting eligibility criteria (Section 9.2.2.1.1.) will be included.

9.2.3.1.2 Clinical presentation, course and outcomes – including risk factors – in all children and adults (secondary objective #1)

All children and adults under clinical surveillance will be included.

Using a case-control analytic approach for risk factor analyses, the power to detect a doubling in the odds of mild, severe or fatal (in-hospital and post-discharge) COVID-19, assuming 5% or 10% prevalence of the risk factor in question, and equal numbers of cases and controls, is summarized in the table below for different sample sizes.

Prevalence of risk factor in controls	N SARS-CoV-2 positive (cases)	N SARS-CoV-2 negative (controls)	Power
5%	100	100	23%
	250	250	50%
	500	500	79%
	750	750	92%
	1000	1000	97%
10%	100	100	38%
	250	250	75%
	500	500	96%
	750	750	100%
	1000	1000	100%

Using a cohort analysis approach for risk factor analyses, the power of the analysis to detect a doubling in risk of mild, severe or fatal (in-hospital or post-discharge) COVID-19 is shown in the table below. This assumes a 5% significance level, a range of mortality rates and 5% or 10% risk factor prevalence in individuals without the respective outcome.

5% risk factor prevalence			10% risk factor prevalence		
% deaths	N	Power	% deaths	N	Power
2%	500	3%	2%	500	6%
	1000	5%		1000	13%
	2500	14%		2500	39%
	5000	34%		5000	76%
	7500	54%		7500	92%
	10000	70%		10000	98%
5%	500	6%	5%	500	17%
	1000	14%		1000	39%
	2500	44%		2500	85%
	5000	80%		5000	99%
	7500	95%		7500	100%
	10000	99%		10000	100%
10%	500	15%	10%	500	38%
	1000	33%		1000	72%
	2500	78%		2500	99%
	5000	98%		5000	100%
	7500	100%		7500	100%

5% risk factor prevalence			10% risk factor prevalence		
% deaths	N	Power	% deaths	N	Power
	10000	100%		10000	100%

N=cohort size, i.e. total number of COVID-19 cases

% deaths is among the unexposed but since the prevalence of exposure is <10% this will correspond approximately to the death rate among COVID-19 patients as a whole

9.2.3.1.3 Clinical presentation, course and outcomes – including risk of death in the inpatient and post-discharge periods – in highly vulnerable adults and children (secondary objective #1)

The paediatric cohort focusing on a subpopulation of higher and lower vulnerable adults and children will include 300 children with WHO defined severe acute malnutrition and 300 children without severe acute malnutrition. Children will not be excluded if they have additional comorbidities (such as HIV). Similarly, the higher and lower vulnerability adult cohort aims to recruit a total of 600 (300 individuals with HIV or chronic non-communicable diseases and 300 individuals without these conditions). Both the paediatric and adult cohort will be followed for 180-days after enrollment and will receive monthly follow-up visits. This stratification is used to optimize statistical power, while minimizing the number of COVID-19 patients exposed to the research protocol.

The sample size calculations are based on the ability to estimate the effect of host vulnerabilities on COVID-19 associated mortality and this aim requires the most participants to achieve statistical power.

For the paediatric cohort, the sample size calculation is conducted for a comparison between children with and without severe acute malnutrition. We assume 80% power, and alpha of 0.05 and that children without malnutrition will have mortality rate of 5% during the 180-days follow-up. Data from the CHAIN Network suggest that children presenting with severe malnutrition typically experience a 3-fold increased risk in mortality compared children without the condition across a broad range of acute illnesses. Therefore, 226 severely malnourished and 226 not severely malnourished children will allow us to detect a slightly conservative estimate of a 2.7-fold increase in risk associated with malnutrition. Accounting for a 20% loss to follow-up, this would yield a total sample size of 600 children, approximately 6-per week per-site.

For the adult cohort, the sample size calculation is conducted for a comparison between adults with and without HIV infection or chronic non-communicable diseases. We assume 80% power, and alpha of 0.05 and that adults without these risk factors will have mortality rate of 3% during the 180-days follow-up. It is reasonable to also expect adults with HIV or chronic non-communicable diseases to experience a 3-fold increased risk in mortality compared to other adults. Again, suggesting that a total sample size of 600 adults should be recruited.

For both cohorts, patients will be recruited consecutively across all sites until the target sample size is achieved.

9.2.3.1.4 Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2

All enrolled patients will be included. Nasopharyngeal and faecal swabs will be collected at monthly follow-up visits for the duration of the 180 day follow-up. Participants will be asked to participate in fecal rectal swabbing in the clinical, and swabs will be stored at -80ºC in appropriate medium for viral culture within 30 minutes of collection. These swabs will have SARS-CoV-2 PCR and viral culture performed at a later date, and will be used to calculate monthly prevalence of SARS-CoV-2 shedding among included participants. The potential for fecal shedding to contribute to viral transmission will be assessed by comparing PCR to viral culture in an effort to understand if the prolonged faecal shedding that has been documented among children and some adults is viable virus or simply viral fragments unlikely to result in further disease transmission.

9.2.3.1.5 Micronutrient studies: vitamin D and iron status

Plasma samples will be collected in asymptomatic and hospitalized children/adults with COVID-19 and also from healthcare workers. The following measures of vitamin D and iron status will be assayed in stored plasma samples (300ul) at the KWTRP laboratories: 25-hydroxyvitamin D (25OHD), ferritin, iron, transferrin, soluble transferrin receptor and hepcidin.

9.2.3.2 Health services assessments

Purposeful sampling will be used to identify senior and junior staff with a variety of roles from different professions and different hospitals focused on maximizing the diversity of respondents. This sampling approach does not aim to ensure those interviewed are statistically representative of all health workers, instead it seeks to ensure multiple viewpoints are explored to uncover a wide range of challenges In this approach it is common to stop including more respondents when little new information is being gained, often this is after including 20-30 respondents.

9.3 Procedures – Clinical surveillance and health services studies

9.3.1 Clinical surveillance

9.3.1.1 Screening and enrollment

The CHAIN research staff will work with the MOH staff to identify suspected cases and collect nasopharyngeal swabs for COVID-19 surveillance in accordance with MOH and CIN protocols. CHAIN research staff will work with health facility staff to conduct surveillance for SARS-CoV-2-associated multisystem inflammatory syndrome, including collection of blood samples among suspected cases for diagnostic testing. Suspected COVID-19 adult and paediatric cases will then be screened for eligibility to the CHAIN-COVID cohort against the criteria described in section 9.2.2, and full written consent will be taken from adults. The parents or legal guardians of eligible children will be asked to provide consent, and children aged 13-17 years will be asked to provide documented assent. Emergency assent will be sought for individuals who are clinically ill at

presentation to the health facility. The timing of consent, and subsequent data collection will be coordinated with MOH staff to ensure that research procedures do not delay, disrupt or replicate emergent care. The number of suspected cases recruited each week will be subject to a dynamic restriction coordinated by the central CHAIN team in Nairobi and based on the anticipated ratio of positive to negative test results. Data from other setting suggest, and early data from CHAIN suggests that approximately 1 in 10 tests are likely to be positive.

After consent has been taken, enrolment data and samples will be collected (Appendix 20.4.1). All enrolled participants will be followed until their test result is returned. Enrolled participants who test negative will have completed the study.

Case investigation forms may be used to identify individuals that have undergone COVID-19 RT PCR testing. Ethical approval to collect clinical and demographic data from case investigation forms is sought through this protocol; individual consent will not be sought to collect data from case investigation forms.

9.3.1.2 Assessment

Baseline data of prognostic importance, including demographic and social information, a detailed clinical examination, and measurement of vital signs, including pulse oximetry, will be collected using a standard proforma. These standardized forms will be harmonized with the CIN surveillance tools to eliminate repetition. Anthropometry will be performed (MUAC, subscapular skin fold thickness, weight and length).

In addition to the nasopharyngeal swab collected for SARS-CoV-2 testing, a research blood sample (up to 5 millilitres) will be collected together with the routine clinical blood draw. Rectal swabs and faecal samples will also be obtained from all participants including adults. At admission, results of investigations performed for clinical care (complete blood count [CBC], biochemistry, glucose, provider-initiated HIV testing and counselling according to national guidelines, a detailed history of engagement in HIV services including antiretroviral and cotrimoxazole exposure, and any other routine laboratory investigations) will be utilised by the study. When the results of any of the clinically indicated tests are available, they will be returned to site clinicians caring for the patient. Patients and their families with newly diagnosed infections will be referred to their local HIV Care Clinic for follow-up.

Table 3. Study course, data collection and sample collection for children and adults admitted to hospital

	SCREENING & ELIGIBILTY	**ENROLMENT**	**DAILY INPATIENT REVIEW**	**DAY 2**	**DAY 5**	**MONTH 1,2,3,4,5,6**	**DISCHARGE**	**DEATH**

MOH/CIN SURVIELLANCE	X							
NP SWAB	X			X	X	X	X	
STANDARD CASE MANAGEMENT [a]	X	X	X	X	X	X	X	
GIVE STUDY INFORMATION	X							
INFORMED CONSENT	X							
ANTHROPOMETRY		X	X	X	X	X	X	
DATA COLLECTION[b]		X	X	X	X	X	X	X
FAECAL SAMPLE		X		X	X	X	X	
RECTAL SWAB		X		X	X	X	X	
BLOOD SAMPLE		X		X	X	X	X	

[a]According to national guidelines

[b]Abstraction/ collection of medical chart data and laboratory test results

During admission, participants will be reviewed daily and clinical features, progress and treatment received recorded on a structured case report form. In the event of death in hospital, a standard cause of death (verbal autopsy) tool will be completed using the medical notes. Any additional tests performed for clinical management (for example, blood culture, blood gases, renal and liver function), will be recorded by the study. When clinical blood draws are scheduled for the same the day, research samples will be obtained from the same draw. If no clinical blood draw is anticipated the research blood draw will be performed, and results will be made available to the child's clinical care team. At discharge, anthropometry, a clinical assessment and blood, rectal swab and whole stool collected.

All participants will have a standardized vital status, clinical data and sample set collection at day 2 & 5 and months 1,2,3,4,5 and 6 after enrolment. It is anticipated that the 2- and 5-day assessments will be completed in the facility, and the monthly visits will be conducted as an outpatient. However, all timepoints will be standardized so that they may be completed as either an in- or outpatient review. If any of these visits become contraindicated under Kenyan national COVID policy, they will be converted to telephone interviews where vital status is collected but in person contact is not made. If the participant dies in the community a WHO standardized verbal autopsy will be completed by a trained staff member.

9.3.1.3 Clinical care

Sites will be encouraged to follow national treatment guidelines for managing the participants suspected/confirmed COVID-19 and any other comorbidities. Whilst in hospital, participants will be reviewed daily by study clinicians, working together with the hospital team. This will ensure that at least a minimum standard of care, based on Kenyan National guidelines, is provided to all study participants. Any clinically relevant laboratory test (per guidelines) will be made available. At discharge or at follow up, participants will be referred to existing nutrition services for outpatient therapeutic or supplementary feeding according to national policy, WHO guidelines and other clinics for additional conditions identified.

9.3.1.4 Data collection

Data will be recorded on a standardised CRF (Appendix 20.4.1 and 20.4.7) in use at every site by trained study staff or the relevant data fields extracted from existing electronic clinical surveillance databases. The data from all sites will be held locally and uploaded to the secure central CHAIN/CIN Network server in Nairobi. This will be overseen by the central Data Manager who will run regular reconciliation to derive the final study database. Access to the study database will be restricted and password protected.

An internal request will be made to KWTRP-Kilifi for COVID-19 case investigation form data to identify individuals that have been tested for COVID-19. Case investigation data will be reviewed to assess age, admission status and for collection of clinical and demographic data for risk factor analyses using a case-control approach.

The data management system will generate automated queries and the data manager will generate manual queries. All queries will be passed through the study coordinator and clarified by the investigators and field staff with clear documentation. The database will maintain an audit trail.

The data management team will adapt analytic methods developed to support routine data management processes including near real-time dashboards currently in use within the CIN to report morbidity, mortality and quality of care indicators for use at facility, county, and national level for monitoring the epidemic and planning for resources needs.

9.3.1.5 Sample collection and processing

Laboratory assays will be a panel of tests done in real-time locally at a designated accredited laboratory, and stored for pooled analyses for the cohort.

Standardised laboratory SOPs will be followed at each site to ensure comparability. The results of abnormal or relevant tests will be made available to clinicians managing the patients at all review time points. In accordance the sites laboratory capacities and the specific sub-studies being run at each the blood test that will be run vary by site. The site-specific samples are outlined in the Table 43 below.

Similar to other enrollments, children and adolescents with physical symptoms consistent with the multisystem inflammatory syndrome case definition (Section 9.2.2) at admission will have blood samples collected and processed for serum, EDTA plasma and cells to examine COVID-19 serology, organ function and inflammatory responses for diagnostic purposes. Research samples that can be used to examine host genetics and transcriptional responses (e.g. Paxgene/RNAlater) will also be collected from these suspected multisystem inflammatory syndrome patients. Samples may be added to sample sets being processed overseas where facilities are unavailable in Kenya or harmonisation of assays between centres is required, in order to better understand this syndrome and its consequences.

In addition to the nasopharyngeal swab collected for SARS CoV-2 testing, a research blood sample will be collected together with the routine clinical blood draw to minimize the patient's discomfort. The volume of blood taken will be up to a maximum of **5ml** total. Rectal swabs and faecal sample will also be obtained from all participants. Storage aliquots will be processed by the site laboratory and the products will be stored at -80˚C for shipping to the CHAIN repository in Kilifi, Kenya. The tests expected be run on stored blood samples in a nested case control analysis are outlined in Table 5. Not all tests will be run on samples from all participants. Rectal swabs are easily obtained on a high proportion of participants, making them optimal for tests that do not require a large volume of stool. Stool samples are difficult to obtain at every time point, but are preferred for some laboratory procedures. Therefore this protocol includes both rectal swabs and faecal samples. Analyses will include molecular detection of pathogen nucleic acids, inflammatory markers and markers of organ disfunction.

Stored samples will be shipped to the CHAIN sample biorepository at the KEMRI/Wellcome Trust Research Programme in Kenya to be stored as permitted by local regulatory authorities. These analyses will be undertaken in Kilifi, or where facilities or expertise is unavailable for example in advanced transcriptomics, shipped to network members and collaborators laboratories, including at the University of Oxford, UK, the University of Washington, USA and University of Toronto, Canada. Samples shipped overseas will contain no personally identifying information.

Table 4. Samples to be taken and immediately processed or stored.

Sample	Test	Admission	Day 2	Day 5	Months 1,2,3,4,5,6	Discharge
NP swab	SAR CoV-2 testing	Surveillance	Research	Research	Research	Research
Blood	CBC	Clinical	Research	Research	Research	Clinical
Blood	Biochem	Clinical	Research	Research	Research	Clinical
Blood	Glucose	Clinical	Research	Research	Research	Clinical

Blood	Malaria RDT	Clinical				Clinical
Blood	HIV	Clinical				
Blood	Plasma Storage	Research	Research	Research	Research	Research
Blood	Serum Storage	Research	Research	Research	Research	Research
Blood	Whole blood Storage	Research	Research	Research	Research	Research
Dried blood spot	Storage	Research	Research	Research	Research	Research
Rectal swab	Stored for SARS CoV-2 Culture	Research	Research	Research	Research	Research
Rectal Swab	Stored for COVID-19 PCR	Research	Research	Research	Research	Research
Stool	Stored for SARS CoV-2 Culture	Research	Research	Research	Research	Research

Table 5: Laboratory tests to be performed on stored blood samples taken at any site after selection as a case or control.

TEST	SAMPLE TYPE
Biochemistry and markers of organ function including renal, hepatic and cardiac function	Plasma
Cytokines & chemokines – multiplex bead array or ELISA examining common inflammatory, lymphocyte, monocyte and neutrophil responses	Serum
Proteomics and Metabolomics – LCMS, HPLC, NMR to identify proteins and metabolites associated with clinical progression and outcomes	Serum
Vitamins, micronutrients, macronutrients (amino acids etc)	Serum
SARS COV-2 antibody testing	Serum/DBS
PBMCS – multiparameter flow cytometry to determine circulating immune cell surface markers	EDTA

Molecular pathogen detection – Taqman card array, singleplex PCR and pathogen rRNA sequencing to identify co-infections	EDTA
SARS CoV-2 PCR and culture	Stool & Rectal swabs

To determine the viability of SARS CoV-2 in faecal samples, 100 enrolment and 100 30-day faecal samples, which have viral DNA detected by PCR, will be randomly selected by an independent scientist for viral culture in an appropriate level biosafety facility in Kenya. A similar selection and analysis will be performed on the rectal swabs collected from these participants.

9.3.2 Health services assessments

During the study period, research staff at the COVID-19 clinical surveillance hospitals (Table 2) will conduct a health care capacity monitoring audit weekly, bi-weekly or monthly as appropriate and care will be taken to make sure the process does not interfere with routine operations of managers and frontline staff.

The research staff will work with hospital teams to track how the hospital is being affected by the COVID-19 response more widely (e.g. whether referral systems are operational, ability to provide routine services etc.). The regular audit will utilize tools that are under development by the Ministry of Health to record a systemic observation of current capacity and will include essential medication availability, essential equipment availability and utilization (including oxygen, high flow oxygen, CPAP, ventilators, intravenous access tools, imaging capacity), human resources for health capacity, current discharge criteria, the distribution/awareness of updated COVID-19 guidance when it becomes available, and include basic semi-quantitative/ qualitative evaluations of health workers familiarity and confidence in undertaking key procedures (e.g. use of PPE or CPAP / ventilators). It will also examine up-referral (transfer to higher level facilities), down-referral (transfer from higher level facilities and data on costs. Where appropriate images of equipment, organizational arrangements and other resources that do not include healthworkers or patients may be used to illustrate hospitals' responses (eg. images of their triage station or of sign-posting for zones where PPE must be used or of the type of ventilator in use).

Essential medication will be assessed at the hospital level (i.e. in the pharmacy), all other assessments will done on in the newborn, paediatric and adult medical care wards, the maternity unit, the admitting facility (emergency room) and any additional ward delivering care to suspected or confirmed cases of COVID-19.

Interviews and small group discussions to help identify the challenges of providing and sustaining services will be conducted with respondents after the purpose of the interview/discussion has been explained to them and with their permission / consent. It will be clear that participation is entirely voluntary and that any information shared will

be confidential and that their name will not be used in any report. Interviews / discussions will take place in a location that preserves confidentiality and at a time that is convenient to the respondent. Interviewers will use a guide such as the one provided in Appendix 20.4.7. We expect these conversations to take 30-60 minutes but they may often be shorter. Due to ongoing travel restrictions linked to the COVID-19 epidemic some interviews / discussions may take place online with the permission / consent of the respondent.

9.3.2.1 Data collection

Data will be entered electronically into mobile device-based REDCap standardized forms. These forms will be adapted from the Ministry of Health and WHO COVID-19 assessment tools in addition to existing tools that have been used in previous surveys. Respondents such as nurse in charge of adult medical ward, pharmacist and hospital accountant will be purposely identified to provide information

9.4 Data analysis – Clinical surveillance and health services assessment

9.4.1 Clinical surveillance

9.4.1.1 Primary objective. Burden of COVID-19

Secondary objective 1. Clinical/ demographic characteristics of cases, including risk factors

Routine data for children admitted to hospitals within the CIN include patient biodata, residence, information gathered during clinical assessment, admission and discharge diagnoses, treatments, and outcome (survival or death). Categorical data will be tabulated and summarised as proportions, whereas continuous variables will be reported as mean (SD) or median (IQR) as appropriate. Univariable and multivariable logistic regression models will be fitted to examine associations with outcomes of interest, e.g., mild COVID-19 versus severe COVID-19 and mortality for demographic and clinical characteristics with at least 50% of data available. We will calculate the monthly five-year age-specific incidence of suspected or confirmed moderate-severe COVID-19 in the catchment populations served by the study hospitals by dividing the monthly number of children admitted with pneumonia in the CIN hospitals from the estimated hospital catchment populations by the mid-year population of the respective age group from the same area (74). Similar analyses will examine the age-specific incidence rate of suspected or confirmed moderate-severe COVID-19 among admitted children using the total admissions for the respective age bands as the denominator.

9.4.1.2 Secondary objective 1. Risk of death in the inpatient and post-discharge periods among adults and children with SARS-CoV-2 and underlying vulnerabilities

In order to estimate the contribution of underlying vulnerabilities to COVID-19 mortality , the data from all sites will be combined into a paediatric (under 15 years of age) and separate adult cohort. The primary analysis will compare the mortality in specific subgroups of interest (HIV infected adults, and severely malnourished children, to comparable individuals without these conditions/comorbidities. Specifically, the relative risk of mortality during follow-up will be calculated in multivariable Cox proportional hazard regression

9.4.1.3 Secondary objective 1. Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2

Secondary endpoints will be the proportion of COVID-19 patients with SARS CoV-2 shedding in stool and nasopharyngeal swabs at 1, 2, 3, 4, 5 and 6 months after enrolment. Risk factors for prolonged faecal shedding will explored using multivariate generalized linear models. These risk factors will include baseline clinical status and demographic, clinical therapies administered, duration of illness and peak severity of illness.

To determine the potential importance of *SARS CoV*-2 faecal shedding to the onward transmission of the virus, a subset of faecal samples, rectal swab and nasopharyngeal swabs will be selected from storage and viral culture will be performed. The potential for faecal shedding to contribute to viral transmission will be assessed by comparing PCR to viral culture in an effort to understand if the prolonged faecal shedding that has been documented among children and some adults is viable virus or simply viral fragments unlikely to result in further disease transmission. The proportion of enrolment and 30-day samples from which live virus can be culture will be estimated with 95% confidence intervals calculated under a binomial distribution

9.4.1.4 Secondary objective 2. Trends in hospitalization and mortality due to all causes and pneumonia in adults

Negative binomial regression model of admission incidence on calendar year and month over the period 2016, 2018 and 2019 will be used to project pneumonia and all-cause incidence of hospitalization and death for 2020. The year 2017 will be excluded from the model because of doctors' and nurses' strike that disrupted inpatient services for most of 2017. Deviance goodness-of-fit test, z-score test for overdispersion, AIC and BIC statistics, and a comparison of predicted and observed hospital admissions will be used to assess the model fit. The resulting model will be used to project the expected number of admissions and deaths to KCH in 2020 and corresponding prediction intervals will be used to assess the uncertainty around the predictions. Observed vs. expected admissions and deaths in 2020 will be compared.

9.4.2 Health services assessment

Categorical data will be tabulated and summarised as proportions, whereas continuous variables will be reported as medians (IQR).

Data from interviews / discussions will be captured using interviewer's written notes and audio files if the respondent gives permission for this. All respondents will be given a specific and unique code that is linked to the interview data. A list of the respondents details (eg. profession, age, facility) will be kept that provides a link to these codes but will only be accessible to specific, named investigators and this list will be stored in a separate, secure location to the interview data. All interview data will be fully transcried into Word files, labelled with the unique code, and stored in password protected servers managed by KEMRI-Wellcome. The interview data will be imported into NVivo 10 software for thematic analysis aimed at identifying the key challenges faced by health workers in providing COVID related and routine services.

10 Virological surveillance studies

10.1 Linked objectives

- To estimate the burden of COVID-19 and prevalence of exposure to SARS-CoV-2

10.2 Design and methodology – Virological surveillance studies

10.2.1 Sites

Two studies will contribute to virological surveillance:

(1) A longitudinal study will be conducted among HCW at the facilities listed below. Additional health facilities will be involved if they are recommended by the Ministry of Health or Counties, have an interest in engaging and there is capacity to include them.
   - Kilifi County Hospital
   - Kenyatta National Hospital
   - Coast General Teaching and Referral Hospital
   - Mbagathi County Hospital
   - Jaramogi Oginga Odinga Teaching and Referral Hospital
   - Aga Khan University Hospital
   - Busia County Referral Hospital
   - Kocholia Sub-County Hospital
   - Alupe Sub-County Hospital

(2) A longitudinal study will be conducted among non-healthcare frontline staff at companies/ sectors such as Kenya Ports Authority (Mombasa), Kenya Airports Authority (Nairobi), Kenya Airways (Nairobi), Kenya Prison Services and truckers (designated testing sites in Kilifi, Mombasa, Taita Taveta, Busia and Nairobi Counties). Companies/ sectors will be chosen with the approval and assistance of the Ministry of Health. A second and third survey will be conducted three and six months after the first, respectively.

10.2.2 Study populations

10.2.2.1 HCW virological surveillance

We plan to recruit the following HCW of all cadres including:

a) those in direct contact with patients e.g. nurses, doctors, clinical officers, porters etc.,
b) those not in direct contact with patients e.g. laboratory staff and non-clinical staff e.g. administrators

Inclusion criteria

- 18 years and above

- Participant is willing and able to give informed consent for participation in the study and agrees with the study and its conduct

Exclusion criteria

The participant may not enter the study if ANY of the following apply:

- Inability to be followed up for the study period
- Declines to give consent

10.2.2.2 Virological surveillance in other frontline staff

We will seek to include staff of all cadres at the selected companies/ organizations/ sectors, including casual employees and contractors.

Inclusion criteria

- Aged ≥18 years
- Willing to provide consent

Exclusion criterion

- Medical contraindication for venipuncture and nasal sample collection

10.2.3 Sampling

10.2.3.1 HCW virological surveillance

The estimated number of frontline HCW at the study sites is 9,000 of whom we estimate up to 1,500 will take part. The table below illustrates the precision obtained in prevalence estimates across a range of sample sizes and prevalences.

	Prevalence (%)					
	1%	2%	5%	10%	20%	50%
Precision (+/–)	n	n	n	n	n	n
0.01	381	753	1825	3458	6147	9604
0.02	96	189	457	865	1537	2401
0.05	16	31	73	139	246	385
0.1	4	8	19	35	62	97
0.2	1	2	5	9	16	25

10.2.3.2 Virological surveillance in other frontline staff

For each organisation/ sector we will seek a list of employee ID numbers together with staff characteristics and will undertake a stratified sampling scheme to ensure adequate representation of age in three strata, of sex, and of blue-collar, office and managerial workers. If not feasible to undertake stratified sampling (e.g. for truckers) we will enrol a convenience sample. We will target **700 staff** at each organisation/ sector at each survey. That sample size was selected to generate prevalence estimates with reasonable precision. For example, 700 participants in one age stratum (across the

three organizations/ sectors) would be sufficient to estimate 2% prevalence of SARS-CoV-2 infection within a ±1% margin.

10.3 Procedures – Virological surveillance

10.3.1 Data collection

HCW and non-healthcare frontline workers will be screened against the criteria in Section 10.2.2. Individuals meeting eligibility criteria will be consented.

10.3.1.1 HCW virological surveillance

We will work with the respective health facility and/or County administrations to obtain lists of all HCW who would be eligible to participate in the study. Where healthcare workers are transferred from their health facility of enrollment, they may be invited back to their health facility of enrollment for data collection.

Personal data will be collected on the date of sampling, including the name and ID of the participant, age/dob, sex, cadre of staff, sublocation of residence and current symptoms (Appendix 20.4.2).

10.3.1.2 Virological surveillance in other frontline staff

Potential participants will be identified either through the HR department or at testing centres for sectors where testing is directed by MoH (e.g. truckers).

Individuals will be invited to participate. Screening, consenting, data and sample collection will be undertaken at the employee health clinic or other physical location of the participant. The survey will be repeated three and six months later.

Personal data will be collected on the date of sampling, including the name and ID of the participant, age/dob, sex, cadre of staff, sublocation residence and current symptoms (Appendix 20.4.3).

For individuals undertaking MoH-directed testing, consent will not be obtained as sample collection will be conducted as part of the national public health response. Personal data will be collected using the MoH Case Investigation Form as part of the national health response. Secondary use of data collected as part of the national public health response is requested.

10.3.2 Sample collection and processing

In all cases, samples will include (1) NP/OP swabs for RT-PCR testing and (2) 5mls of blood for plasma. The blood sample will be used for serosurveillance (see ‘Serosurveillance’ section).

A single nasal sample will be collected from each participant using a flocked rayon swab placed in viral or universal transport medium (VTM or UTM). Additional samples will not be collected where a sample is collected by the County Rapid Response Team as part of MoH-directed testing. Standard technique will be used for collection of the nasopharyngeal samples (75). Samples will be stored at 2-8 degrees Celsius or -20 degrees Celsius, depending on when testing is expected to occur. Samples will be transported to the KWTRP laboratory for testing. As mentioned previously, the KWTRP

is the designated COVID-19 testing laboratory for the Coast region. Viral RNA will be purified from the nasopharyngeal sample using a commercial kit and analyzed for presence of two or more of the following: envelope (E) gene, replicase-encoding region (ORF1ab/RdRp) and nucleocapsid (NP) gene. The results of the RT-PCR test will be communicated to the participant. Positive results will be reported to the respective County RRT via the KEMRI Director General and MOH, or other protocols.

10.3.2.1 HCW virological surveillance

Where possible, the HCW will undergo repeated sampling every 4 months for up to 12 months.

10.3.2.2 Virological surveillance in other frontline staff

Other frontline staff will undergo a total of three repeated samplings; the second and third samplings will be conducted three and six months after the first sampling, respectively.

10.4 Data analysis – Virological surveillance studies

In all cases, the prevalence of SARS-CoV-2 infection and proportion of symptomatic infections will be estimated. Stratified analyses will examine differences in these indices by location, cadre (for HCW and other frontline staff), age, sex and any other available characteristics.

The cumulative incidence of SARS-CoV-2 infection will be estimated using standard epidemiologic methods.

11 Serosurveillance studies

11.1 Linked objectives

- To estimate the burden of COVID-19 and prevalence of exposure to SARS-CoV-2 (primary objective)

11.2 Design and methodology – Serosurveillance studies

11.2.1 Sites

Six studies will contribute to serological surveillance:

(1) A repeated cross-sectional survey among ANC clients. This study be conducted in the health facilities listed below. Additional health facilities will be involved if they are recommended by the Ministry of Health or Counties, have an interest in engaging and there is capacity to include them.
   - Kenyatta National Hospital
   - Kilifi County Hospital
   - Coast General Teaching and Referral Hospital, Mombasa
   - Mbagathi County Hospital, Nairobi
   - Jaramogi Oginga Odinga Teaching and Referral Hospital, Kisumu
   - Busia County Referral Hospital

(2) A longitudinal study among HCW (sites as described under virological surveillance)

(3) A longitudinal study will be conducted among non-healthcare frontline staff (sites as described under virological surveillance)

(4) Repeated cross-sectional surveys will be conducted among residents of the Kilifi, Nairobi and Manyatta Health and Demographic Surveillance Systems (HDSS) (76-78).

(5) A longitudinal study among asymptomatic RT-PCR-confirmed SARS-CoV-2 infected individuals as reported by the Ministry of Health Emergency Operations Centre (EOC)

(6) A longitudinal study among symptomatic RT-PCR-confirmed SARS-CoV-2 infected hospitalized individuals

(7) A retrospective serosurvey will be conducted using stored samples collected from paediatric and adult patients hospitalized at Kilifi County Hospital who provided consent for storage of samples and use in future research.

11.2.2 Study populations

11.2.2.1 ANC serosurveillance

The study population will include all the mothers attending ANC at one of the four specified referral hospitals.

Inclusion criterion:

- All women attending ANC for the first time who provide a routine ANC blood sample will be included in the study

Exclusion criteria:

- Any woman with a contraindication to venipuncture or who doesn't provide a sample for the routine testing programme at ANC.
- Any mother coming for a follow-up visit who has already had a routine bleed done at her first visit

11.2.2.2 HCW serosurveillance

As described under virological surveillance.

11.2.2.3 Serosurveillance in other non-healthcare frontline staff

As described under virological surveillance.

11.2.2.4 HDSS resident serosurveillance

Inclusion criteria

- Ordinarily HDSS resident of all ages
- Willing to provide consent

Exclusion criteria

- Bleeding disorders and other medical contraindication for venipuncture or capillary blood sample collection.

11.2.2.5 Serosurveillance among asymptomatic infected individuals

Inclusion criteria

This objective will target asymptomatic (at the time of initial assessment) SARS-CoV-2-infected individuals residing within or around Nairobi, Mombasa, or Eldoret City

- SARS-CoV-2-infected individuals
- Willing to provide consent

Exclusion criteria

- Unreachable via mobile telephone
- Currently hospitalised with severe illness
- Deceased
- Current residence beyond a 1-hour commute by road from Nairobi, Mombasa, or Eldoret Central Business District
- Bleeding disorders and other medical contraindication for venipuncture and nasal sample collection

11.2.2.6 Serosurveillance among symptomatic non-severe and severe SARS-CoV-2 infected individuals

Inclusion criteria

This objective will target symptomatic (at the time of initial assessment) SARS-CoV-2-infected patients receiving care as inpatients at Aga Khan University Hospital, Kenyatta National Hospital, Kenyatta University Teaching Research and Referral Hospital, Moi Teaching and Referral Hospital

- SARS-CoV-2-infected individuals
- Willing to provide consent

Exclusion criteria

- Patients who do not provide a routine blood sample for plasma or serum.

11.2.2.7 Retrospective serosurvey among hospitalized children and adults

Inclusion criteria:

- Individuals admitted to KCH paediatric or adult wards
- Provided consent for storage of samples and future use under SSC 1433 since 2009 onwards

- No known active SARS-CoV-2 infection at the time of admission

11.2.3 Sampling

11.2.3.1 ANC serosurveillance

With at least 135 samples *per month from each site* we would be able to estimate the seroprevalence with 3-7% precision (depending on the prevalence itself, Table 6).

Table 6. Precision with which we would be able to estimate a range of seroprevalences if n=135

Estimated seroprevalence	**Estimated precision**	**n (mothers per month at each site)**
3%	3%	135
10%	5%	135
15%	6%	135
20%	7%	135
25%	7%	135

11.2.3.2 HCW serosurveillance

As described under virological surveillance.

11.2.3.3 Serosurveillance in non-healthcare frontline staff

As described under virological surveillance.

11.2.3.4 HDSS resident serosurveillance

For each serosurvey in each HDSS location, we will use the population register to select a random sample of residents across all age groups targeting 850 persons in an age-stratified sample as 50 in each 5-year age band between 15-64 years, 50 among those 65 years and above and 100 in each 5-year age band from 0-14 years. This target sample size will yield 300 participants <15 years which will be enough to estimate 1% seroprevalence with a 2% margin of error. It will also give 500 participants in the 15-64-year-age group which will be enough to estimate a seroprevalence of 3-5% with <5% error margin (79).

11.2.3.5 Serosurveillance among asymptomatic infected individuals

All eligible individuals will be considered for enrolment in the cohort. We anticipate a sample size of approximately 200 for the final analysis accounting for ineligible participants including those who decline to provide consent (25%), and losses to follow up (20%) over the follow-up period. This sample size will allow for the estimation of seroprevalence at each interval survey within a margin of 7% at a 95% confidence interval assuming seroconversion rates of 50%.

11.2.3.6 Serosurveillance among symptomatic non-severe and severe SARS-CoV-2-infected individuals

All eligible individuals will be considered for enrolment in the cohort. We estimate a total of at least 50 eligible samples at the beginning of the study. This number is expected to increase as the epidemic progresses in Kenya.

11.2.3.7 Retrospective serosurvey among hospitalized children and adults

Comprehensive sampling will be undertaken. Approximately 1,600 plasma/ serum samples from adults and children hospitalized at KCH are stored annually under SSC 1433. Sampling will be as follows:

- All serum/ plasma samples collected from January 2020 onwards will undergo anti-SARS-CoV-2 IgG antibody testing
- If the lower bound of the 95% confidence interval (CI) for anti-SARS-CoV-2 IgG seroprevalence is >2% – i.e., greater than the upper bound of the 95% CI for the assay's false positive rate – in January or February 2020 (the period before SARS-CoV-2 was thought to be circulating in Kenya), all samples collected since December 2019 backwards will undergo anti-SARS-CoV-2 IgG antibody testing until there are two consecutive years in which seroprevalence is not higher than expected based on the assay's specificity.
    - In the event that there are resource constraints to test all serum/ plasma samples for anti-SARS-CoV-2 IgG antibodies, samples will be randomly selected for testing. The table below summarizes the margins of error for various monthly seroprevalence estimates given random stratified (adult vs. pediatric) selection of 50% or 75% of samples.
    - To evaluate whether SARS-CoV-2 seropositivity in the period before SARS-CoV-2 was thought to be circulating in Kenya may be due to cross-reactivity, all serum/ plasma samples tested for anti-SARS-CoV-2 IgG will also be tested for antibodies to eCoVs.
    - To evaluate whether SARS-CoV-2 seropositivity in the period before the virus was thought to be circulating in Kenya may be due to SARS-CoV-2 infection, all samples collected in months when the lower bound of the 95% confidence interval for anti-SARS-CoV-2 IgG seropositivity is >2%, and all samples in the 3 months preceding the last month when the lower bound of the the 95% CI for seropositivity is >2%, will undergo nucleic acid testing.

% sampled (monthly N)	95% CI			
	2% seroprevalence	5% seroprevalence	10% seroprevalence	20% seroprevalence
50% (33)	+/- 6%	+/- 8%	+/- 10%	+/- 14%
75% (50)	+/- 4%	+/- 7%	+/- 8%	+/- 11%

11.3 Procedures – Serosurveillance studies

11.3.1 Data collection

With the exception of ANC serosurveillance, which will not enroll participants, individuals will be screened against the criteria in Section 11.2.2. Individuals meeting eligibility criteria will be consented

11.3.1.1 ANC serosurveillance

The objective is population screening using samples that are already taken for other tests. There is no intention in providing individual SARS-CoV-2 antibody test results to ANC clients. A positive antibody test will indicate past (likely not active) SARS-CoV-2 infection, however, it would be unclear whether this confers any immunity and the duration of immunity is unknown. Therefore, providing antibody test results would not have any benefit to ANC clients or other groups of participants. A waiver of individual informed consent among ANC clients is requested given that the study would use residual blood collected for routine ANC care, i.e., blood will not be collected solely for research purposes. Routine identification data will not be collected. The nurse attending to the mothers at ANC will fill a short data collection form including: Date of collection, client's date of birth, client's sublocation of residence, Trimester of pregnancy or estimated day of delivery, and COVID-like symptoms in the last 1 month (Appendix 20.4.4). A unique number will be used on the patient's data collection form to anonymise the form, no identifiable information will be collected.

11.3.1.2 HCW serosurveillance

As described under virological surveillance.

11.3.1.3 Serosurveillance in non-healthcare frontline workers

As described under virological surveillance.

11.3.1.4 HDSS resident serosurveillance

Written informed consent will be obtained from all eligible residents. A questionnaire will be administered to all consenting participants to obtain demographic (as in section 10.3.1.2) and COVID-19 exposure information, where known (Appendix 20.4.5).

11.3.1.5 Serosurveillance among asymptomatic infected individuals

Case Investigation Forms (Appendix 20.4.1) for all PCR-confirmed SARS-CoV-2-infected individuals as reported by the Ministry of Health will be screened consecutively using assigned serial numbers for eligibility. Mobile telephone contact data will be used to trace potential study participants. Fieldworkers will be engaged through the EOC and Nairobi, Mombasa, and Uasin Gishu County Rapid Response Teams and trained on the study procedures including obtaining informed consent, infection prevention and control, sample collection and handling. Ahead of each visit, the fieldworkers will call study participants and provide details of the study, obtain initial verbal assent, and if successful, schedule an appropriate time for the visit for sample collection. Upon arrival

at the participant's physical location, written informed consent will be sought. Consent for children under 18 years will be obtained from a parent or legal guardian. A questionnaire will be administered to each participant recruited into the investigation capturing residential, demographic, exposure, and clinical information (if these data are not accurately captured in the Ministry of Health Case Investigation Form; Appendix 20.4.6). No additional identification data will be collected.

11.3.1.6 Serosurveillance among symptomatic infected individuals

Clinical records for all PCR-confirmed SARS-CoV-2-infected individuals admitted to the Aga Khan University Hospital, Kenyatta National Hospital, Kenyatta University Teaching Research and Referral Hospital, Moi Teaching and Referral Hospital will be screened for eligibility. For patients who are discharged, mobile telephone contact data will be used to trace potential study participants. Ahead of each visit, the fieldworkers will call study participants and provide details of the study, obtain initial verbal assent, and if successful, invite the study participant to come to the hospital at an appropriate time for sample collection or alternatively schedule a home visit. Upon arrival at the participant's physical location, written informed consent will be sought. Consent for children under 18 years will be obtained from a parent or legal guardian. A questionnaire will be administered to each participant recruited into the investigation capturing residential, demographic, exposure, and clinical information (if these data are not accurately captured in the clinical record; Appendix 20.4.1). No additional identification data will be collected.

11.3.1.7 Retrospective serosurvey among non-COVID hospitalized children and adults

Demographic, clinical and laboratory data will be extracted from the Centre-wide integrated surveillance databases.

11.3.2 Sample collection and processing

For ANC serosurveillance, once the patient's routine blood sample is collected (5ml), the designated lab personnel will transfer not less than **0.5ml** of the blood collected and not more than **2mls** (depending on overall volume of the blood draw) to a vacutainer.

For the serosurveillance studies listed below, **5ml** of blood will be collected from participants aged 5 years and above, or **2-5 ml** for those aged below 5 years. The frequency of blood sample collection per participant will be as follows:

(1) HCW serosurveillance – One blood sample collected approximately once every 3 months (4 samples total over one year)
(2) Non-healthcare frontline worker serosurveillance – One blood sample collected at enrollment, three months post-enrollment and six months post-enrollment (3 samples total over 6 months). Additional blood samples will not be collected where blood samples are collected by the County Rapid Response Team as part of MoH-directed testing.
(3) HDSS residents – A single 5ml venous blood sample. In addition to venous blood, DBS samples will be collected from a conveniently sampled sub-set of

10% of participants at each site who provide consent. Blood spots will be collected using a filter card and a volumetric absorptive microsampling device (Mitra device). The total volume of blood spots to be collected per participant is about 100µL.

(4) Asymptomatic cases – A blood sample will be collected 2 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 6 months, 9 months and 12 months after diagnosis (8 samples total over one year)
(5) Symptomatic cases – A blood sample will be collected 2 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 6 months, 9 months and 12 months after diagnosis (8 samples total over one year)

In all cases, blood samples will be labeled with a unique identifier linked to individual participants' data collection form. Samples will be centrifuged and serum separated within 24 hours of collection. If collected at sites other than Kilifi, serum samples will be stored at -20°C and transported to the KWTRP laboratories on dry ice. If collected in Kilifi the samples may be tested immediately after serum is separated or they may be stored for testing at a later date.

For the retrospective serosurvey among hospitalized patients, one aliquot of plasma or serum will be retrieved from the biobank. A single aliquot is expected to contain ≤1000 µl of plasma or serum. The aliquot will be thawed per standard operating procedures.

Serum or plasma samples will be screened for the presence of COVID-19 virus specific IgM and IgG antibodies using an enzyme linked immunosorbent assay (ELISA; please see section 14). For either IgM or IgG positive samples, a plaque reduction neutralization test (PRNT) will be done to confirm the presence of SARS-CoV-2 neutralizing antibodies.

For SARS-CoV-2 serosurveillance among HDSS residents, blood group testing will also be performed.

For the retrospective survey, testing for SARS-CoV-2 RNA using archived samples (blood products, urine, cerebrospinal fluid) will be performed as specified in the sampling section (11.2.3.7). Viral RNA will be purified from the sample using a commercial kit and analyzed for presence of two or more of the following: SARS-CoV-2 envelope (E) gene, replicase-encoding region (ORF1ab/RdRp) and nucleocapsid (NP) gene.

11.4 Data analysis – Serosurveillance studies

The prevalence of exposure to SARS-CoV-2 will be calculated as a simple proportion of the samples tested that were positive for IgM or IgG to SARS-CoV-2. Prevalence estimates will be stratified by characteristics such as site, sublocation, age, sex (except ANC serosurveillance), trimester (ANC serosurveillance only) and blood group (HDSS serosurveillance).Seroprevalence over time will be presented.

The main outcomes for the HDSS serosurveillance are the age specific attack rate, the age specific cumulative incidence IgG/IgM antibodies to SARS-CoV-2 and the proportion of asymptomatic COVID-19 cases.

Summary data on perceptions of dried blood spot sampling for serosurveillance will be generated, as well as assay validation data (Section 14).

Where samples are collected as part of MoH-directed testing, secondary use of data collected as part of the national public health response is requested.

12 Host genetics studies

12.1 Linked objectives

- To investigate host genetic determinants of susceptibility to COVID-19, and molecular mechanisms of SARS-CoV-2 severity and death in hospitalized children and adults with long-term biomass exposure and severe undernutrition (secondary objective #4)

12.2 Design and methodology – Host genetics studies

12.2.1 Sites

Target gene analyses and genome-wide studies will be conducted using data and samples collected in the area surrounding the Center for Geographic Medicine Research - Coast (CGMR-C), Kilifi, Kenya. The laboratory work will be conducted at the CGMRC-C in Kenya, the Rockefeller University in the United States, and the Mahidol Oxford Tropical Medicine Research Unit in Thailand.

12.2.2 Study populations

The target gene analyses will include genetic data and/or material from participants from within the area served by the Kilifi Health and Demographic Surveillance System (KHDSS) who have already been involved in studies conducted under protocol SSC 3420 (“Epidemiological and functional studies of candidate malaria-protective polymorphisms”; genetic data only), and SSC 3257 (“Genetics of iron status and susceptibility to childhood infections study”; genetic data and material).

Both the target gene analysis and the genome-wide study will also include participants from COVID-19 surveillance work being carried within the KHDSS as described in this protocol, as well as those participating in the COPCOV and SOLIDARITY drug trials in Kilifi, Mombasa, Nairobi and Kisumu. We will target COVID-19 cases with asymptomatic, mild and severe manifestations of the disease, as well as healthy controls.

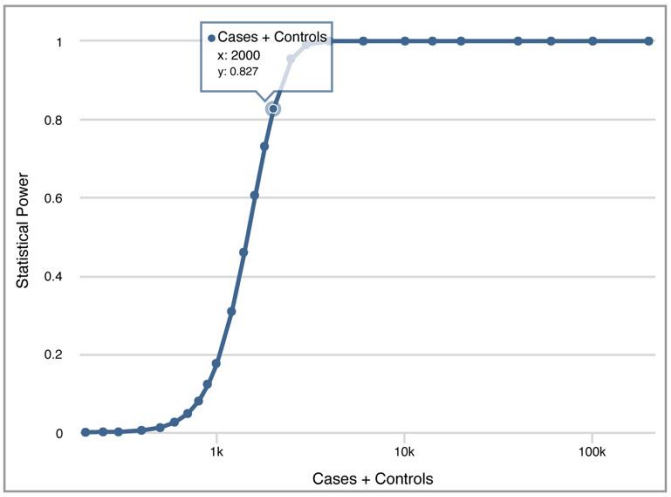
12.2.3 Sampling

We will collect and cryopreserve whole blood sample aliquots from study participants for establishing an archive of DNA and RNA samples for the host genetics studies. We aim to collect samples from 500 cases and controls or more.

The sample size determination for this study is entirely pragmatic, and is based on the number of samples and data that will be available to us. The samples we collect here

will be used in host genetics studies conducted at the KWTRP, and will also be contributed to the COVID Human Genetic Effort international consortium, which aims to collect a minimum of 2000 cases and controls globally for whole genome-genotyping and exome sequencing. This sample size of 2000 cases and controls gives greater than 80% power to detect genome-wide significant ($p < 5x10^{-8}$) common genetic variants (disease allele frequency of ~0.35) associated with disease susceptibility with a genotype relative risk of 1.6 or greater (illustrated in graph **(a)** below). This assumes an additive disease model, where the risk of disease increases with each additional copy of the risk allele, with a disease prevalence of at least 1%. Depending on the phase of the epidemic, the disease prevalence is bound to change, and the table **(b)** below shows the power estimates for disease prevalences ranging from 0.1% to 10%. Power calculation done with the Genetic Association Study Power Calculator interface (80): http://csg.sph.umich.edu/abecasis/gas_power_calculator/index.html.

a



A sample size of 2000 cases and controls gives >80% power to detect genome-wide significant common disease variants with a disease allele frequency of ~0.35, and a genotype relative risk of 1.6

b

Disease Prevalence (%)	Statistical Power (%)
0.1	78.7
0.2	78.9
0.5	79.4
1.0	80.3
2.0	83.0
5.0	87.0
10.0	93.4

Statistical power estimates for a range of disease prevalences, given a sample size of 2000 cases and controls, a disease allele frequency of 0.35, and a genotype relative risk of 1.6

12.3 Procedures – Host genetics studies

12.3.1 Target gene analyses

Using available genetic data from previous studies, polymorphisms in target genes of interest, such as the angiotensin-converting enzyme 2 (ACE2) viral receptor gene, and the transmembrane serine protease 2 co-receptor gene (TMPRSS2), will be analysed for their contribution to COVID-19 susceptibility. Allele frequency differences across populations, and association between these polymorphisms and different disease outcomes will highlight differences in disease manifestation across populations, and correlations with disease severity. The impact of these polymorphisms on variations in intermolecular interactions between the viral spike protein and the ACE2 host receptor will further elucidate the functional consequences of variations in these target genes, which could lead to susceptibility or resistance to SARS-CoV-2 infection.

12.3.2 Genome-wide studies

We will also employ a hypothesis-free approach by studying the association of genome-wide polymorphisms and transcriptomic signatures with different disease outcomes. This approach could identify novel genes involved in the pathophysiological processes that lead to disease onset, highlighting more potential therapeutic targets in both the virus and the host. To achieve this objective, we will collect and cryopreserve up to 2ml of whole blood samples in EDTA tubes from across different surveillance sites and drug trials. Remnant nasopharyngeal swabs from the testing procedures will also be cryopreserved. Genomic DNA and RNA will be extracted from archived blood samples and nasopharyngeal swabs using standard methods utilizing Qiagen kits (Qiagen blood Mini kits for DNA extraction and Qiagen RNeasy Plus Mini kits for RNA extraction from Qiagen, UK. The quantity and quality of the DNA and RNA will be assessed using the Agilent 2100 Bioanalyzer and kits (Agilent Technologies).

Genome-wide genotyping of cases and controls will be done with the dense map Affymetrix SNP6.0 array (>906000 SNPs and >946000 probes for the detection of copy number variation), and results will be analysed with MERLIN software. In parallel, exon sequencing of all cases will be done with SureSelect Enrichment kit Whole exome (38Mb) and Illumina sequencer (76bp), and results will be analysed with MOSAIC software. Whole-genome sequencing will also be conducted in selected cases. For the transcriptomic studies, library prep and RNA sequencing will be conducted on Illumina HiSeq 2500 (commercially outsourced).

All sample processing and target single nucleotide polymorphism (SNP) genotyping will be conducted at the CGMR-C, while genome-wide genotyping and whole-genome sequencing techniques will be conducted at the Rockefeller University in the United States. Whole transcriptome analysis will be commercially outsourced to achieve depth (30-50 million reads, per sample). All genomic data analysis will be conducted at the CGMR-C.

12.4 Data analysis – Host genetics studies

We shall investigate associations between target and genome-wide genotypes and transcriptomes with disease incidence using a case-control approach, comparing SARS-Cov-2 positive cases to negative controls using logistic regression models. Correlations between genotypes and transcriptomes with disease severity will be analysed using linear regression models, applying both a case-control approach, comparing genotypes of severe COVID-19 cases to negative controls, and a case-case approach, where genotypes and transcriptomes of severe cases will be compared to mild or asymptomatic cases. The regression models will be adjusted for age, sex, and known risk factors including comorbidities such as hypertension, diabetes, and cardiovascular disease. Unknown sources of variation in the genomic data, including population structure, will be controlled for by carrying out a principal components analysis and adjusting for the principal components representing the largest amounts of variation in the data.

Expression quantitative trait locus mapping analysis will further be done using the Matrix

eQTL R statistical software package (81) to run linear regression models to test for associations between genome-wide polymorphisms and whole genome differential gene expression. This analysis will highlight potential functional roles of polymorphisms linked with susceptibility to COVID-19.

13 Molecular mechanisms studies

13.1 Linked objectives

- To investigate host genetic determinants of susceptibility to COVID-19, and molecular mechanisms of SARS-CoV-2 severity and death in hospitalized adults with long-term biomass exposure and severe undernutrition (secondary objective #4)

13.2 Design and methodology – Molecular mechanisms studies

These studies will not sample human populations.

13.3 Procedures – Molecular mechanisms studies

Experiments under this section will rely on residual stored samples collected from the surveillance activities described in this protocol. Primary sample collection will not be undertaken to address the questions under this section.

Samples will be collected from individuals with a positive lab diagnosis for SARS-CoV-2.

Respiratory and serum samples collected from each participant at the time of acute disease as well as subsequent follow up time points until a negative result is recorded will be analysed. Samples used will be residues of samples collected for diagnosis or clinical management. Samples from age-matched controls who present with similar symptoms, but who are SARS-CoV-2 negative will also be analysed. Further analyses of control populations will utilise samples obtained from healthy age-matched individuals without any clinical symptoms consistent with COVID-19 disease. At the time of recruitment for the primary studies, clinical and demographic metadata will be obtained from the participant. These metadata will be used for subsequent risk stratification analysis.

To identify the immunopathological mechanisms associated with adverse outcomes (i.e. death or severity of disease that is potentially life-threatening) will propose to adopt a multi-faceted series of systems investigations to identify molecular mechanisms in the respiratory tract and in blood that elevate the risk of death upon infection. We will examine whether exposure to risk factors such as biomass smoke exposure and undernutrition/overnutrition are linked to the pathological mechanisms of SARS-CoV-2-associated severe disease.

To examine responses to SARS-CoV-2 in the airway, we will use untargeted high-performance liquid chromatography-based tandem mass spectrometry to identify and quantify airway proteins that are differentially expressed between cases and controls as well as by exposure to specific risk factors. Simultaneous analysis of the host microbiome will be conducted on these samples to identify whether SARS-CoV-2 leads

to perturbations of airway-resident microbiota or whether the intense airway inflammation that is characteristic of severe COVID-19 illness, induces a leakage of airway microbiota and its associated products into systemic circulation. Both sets of analyses (proteomics and metagenomics) will be conducted in respiratory samples and serum (see detailed methods below). In addition to these analyses, we propose to examine the cellular mechanisms through which SARS-CoV-2 might be driving severe illness. For this analysis, we will use respiratory samples collected from cases and controls to identify specific immune subsets in the respiratory tract and in peripheral blood mononuclear cells.

13.3.1 Sample processing

13.3.1.1 Proteomic analysis of respiratory tract samples and serum from SARS-CoV-2-infected patients

Samples will be centrifuged at 17,000xg for 10 mins at 4°C to obtain cell pellets which will be washed once using PBS and lysed by bead-vortexing for 10 minutes in cell lysis buffer (RLT, Qiagen, Germany). Proteins (as well as DNA and RNA) will be then extracted from the lysate using the AllPrep DNA/RNA/Protein Mini Kit (Qiagen, Germany) following the manufacturer's instructions. The concentration of total protein obtained will be determined using the Bradford assay (Bio-Rad, USA). Thirty micrograms (30µg) of total protein from each sample will be then reduced with 10mM tris(2-carboxyethyl)phosphine (TCEP, Sigma-Aldrich, USA) at 55°C for 1h and subsequently alkylated with 18mM IAA (Sigma-Aldrich, USA) for 30 minutes at room temperature, while keeping the reaction protected from light. Protein precipitation and digestion will be conducted as described in our previous publications (82-84).

13.3.1.2 Metagenomic analysis of airway and blood samples from SARS-CoV-2-infected patients.

Samples will be retrieved from storage, thawed on ice and cell pellets obtained by centrifuging samples for 10 minutes at 14,000 rpm, after which they will be washed once using sterile phosphate buffered saline (PBS). 350ull of a cell lysis buffer (RLT, qiagen) supplemented with beta-mercaptoethanol (1%) will be added to the pellet and vortexed briefly to break up the pellet. Glass beads will be then added to the sample and homogenization will be done by vortexing at maximum speed for 1 min. DNA extraction from the cell homogenate will be done using the AllPrep RNA/DNA/Protein kit (Qiagen), following the manufacturer's instructions. DNA yields will be quantified using a Qubit 2.0 fluorometer (Thermo Fisher).

The V3-V4 hypervariable region of the 16S rRNA gene will be targeted for sequencing. Primers targeting this region will be constructed with Illumina adapter overhang sequences added to the gene-specific primer sequences.

13.3.1.3 Cellular analysis of immune cells in the airway and in systemic circulation

Respiratory or peripheral mononuclear cells will be centrifuged at 17,000xg for 7 minutes, after which 800ul of the supernatant will be removed and discarded. The remaining 200ul will be split into two aliquots of 100ul each. The first aliquot will be used

for neutrophil phenotyping assays and the other will be used for neutrophil phagocytosis assays. 20ul of a pre-constituted cocktail of the following antibodies (from ThermoFisher) will be used to label both aliquots – CD45, CD16, CD14, CD3, CD19, HLA-DR, CD66b, CD11b and a Live-dead marker. With the exception of the live/dead marker, all other antibodies will be diluted 1:100 in FACS buffer. The live/dead marker will be prepared at a 1:1000 dilution in FACS buffer. The phagocytosis functional assays and flow-cytometry data acquisition will be done as previously described (83).

13.4 Data analysis – Molecular mechanisms studies

For the proteomic analysis of respiratory tract samples and serum from SARS-CoV-2-infected patients, raw mass spectrometer files will be analysed by MaxQuant software version 1.6.0.1. by searching against the human Uniprot FASTA database using the Andromeda search engine.

For the metagenomic analysis, product amplification, library preparation and 16S rRNA gene sequencing will be done as described in our previous work (83).

Flow cytometry data from the cellular analysis of immune cells will be analysed using FlowJo software.

14 Antibody assays

We will develop serological assays to detect antibodies against SARS-CoV-2 and use these for the serosurveys and immunological characterization described in this protocol. These assays will include a two-step ELISA method developed by Krammer and colleagues , alternative SARS-CoV-2 Spike-based ELISAs, and a pseudotyped neutralizing antibody assay, among others. Sera from lab-confirmed COVID-19 cases and recombinant monoclonal antibody against the SARS-CoV-2 Spike protein will be used as controls in these assays. International assay standards, whose production is currently being coordinated by the WHO, will be used once available. Confounding by potential cross-reactive antibody responses against other viruses (including NL63, OC43, MERS-CoV and others) will be ruled out by measuring antibody responses against these antigens using similar serological assays. Detailed characterization of antibody responses will include measurement of IgM, IgA and IgG (including IgG sub-classes) isotypes, functional antibody assays (e.g. antibody dependent cell mediated cytotoxicity) and antibody avidity. IgA responses against SARS-CoV-2 antigens will be measured in nasopharyngeal fluid, where available. We will validate the performance of the commercial SARS-CoV-2 IgG immunoassays developed in the Kenyan population. Specificity will be determined using deidentified serum specimens from individuals sampled before SARS-CoV-2 was thought to be circulating in Kenya. To determine assay sensitivity, we will analyse serum specimens from patients who tested RT-PCR positive for SARS-CoV-2 in Kenya. We will compare performance of the commercial assay against the in-house assay using specimens collected in this protocol. We will also compare performance of the in-house assays using DBS.

15 Data management

Data from standardised paper-based tools (Appendix 20.4) will be entered electronically into secure electronic databases with inbuilt checks by trained data clerks or research assistants. All paper records will be kept in a locked filing cabinet at the appropriate site, which is accessed only by the investigators and the study staff. For clinical surveillance of known and suspected COVID-19, all local computer entry and networking programs will be done with coded numbers and initials only and will be password protected. Only the investigators and the clinical monitors will have access to the records. Databases will be held on a dedicated secure server with routine, secure off-site backup. Data access and confidentiality will be overseen by the Manager, ICT department.

Paper records will be stored for 5 years, or 10 years for patient notes, after study completion. When active, records will be stored on site and may be stored off site during the archival period, before destruction. Data in electronic databases will be archived for at least 10 years on KWTRP servers. The database holding contact information for participants consenting to future contact will be maintained indefinitely. De-identified data will be stored indefinitely in the KWTRP Data Repository.

15.1 Data sharing

Data generated from these studies will be shared between the research sites involved and the respective coordinating centre to support cross-site analysis. All systems for sharing data between sites will ensure data security and privacy. De-identified data from individual sites or across the collaboration may be shared with the funder and/or external institutions. All requests for access to study data will be reviewed by the KWTRP data governance committee. Personally identifiable data will not be shared with outside organizations as per KWTRP data sharing guidelines.

15.2 Intellectual property

Any intellectual property rights that arise from the work will be safeguarded according to current KEMRI guidelines and the Industrial Property Act of 2001, sections 32, 58 and 80. The scientific and intellectual contributions of all persons involved in the research will be appropriately acknowledged in all publications and presentations arising from the work.

16 Ethical considerations

All CIN data are de-identified. Some of the activities in this master protocol are approved under a series of annually renewed protocols submitted to KEMRI Scientific and Ethical Review Unit:

Activity	Protocol number
CIN	SSC 3459
Clinical surveillance in Kilifi	SSC 1433 SSC 1999
Investigation of candidate gene polymorphisms	SSC 3420 and SSC 3257

This protocol will be subject to ethical approval from SERU Nairobi, and the applicable institutional ethical committees for non-KEMRI investigators.

Staff with participant contact will receive the appropriate training on personal protection and will be provided with personal protective equipment guided by Ministry of Health, County, Programme, and other applicable institutional clinical and laboratory guidelines. In the event of conflicting guidelines, PPE offering the higher level of protection will be chosen. Studies involving enrollment of human participants will conduct study procedures, including consenting, sample collection and data collection in observance of prevailing MoH and other national guidelines and measures to prevent SARS-CoV-2 infection among study staff and participants such as physical distancing and hand hygiene practices.

The study will maintain ethical standards through internal and external training, monitoring and standardisation of procedures. All investigators will have been required to complete research ethics training. Lead investigators for each objective are listed in Appendix 1 for ease of reference on individuals responsible for overall oversight and scientific coordination for the various activities included in this master protocol.

As the sub-studies described under this protocol are observational, participation is not expected to introduce any exclusions to participate in therapeutic or prophylactic clincial trials. However, enrollment of participants in therapeutic or prophylactic clinical trials may preclude participation in the hospitalized COVID cohort and serosurveillance studies as treatments may impact the clinical course of disease or immune responses. As with all studies, participation in the sub-studies described under this protocol is voluntary and participants may choose to withdraw from any of the sub-studies in order to participate in therapeutic or prophylactic clinical trials. Study investigators will not impede participation of enrolled individuals in therapeutic or prophylactic clinical trials. Both the surveillance and the cohort provide a platform that can be transitioned trial use as we have previously done in both CIN (SSC 3459) and CHAIN (KEMRI/CGMRC/CSC/054:3318).

In the specific case of interviews / discussions it will be clear to respondents that their participation is voluntary and they will be asked for permission / consent. They can ask to terminate any aspect of their participation at any stage and every effort will be made to ensure their confidentiality is preserved. In particular, no individual’s name nor facility name will be used in any report. Every effort will also be made to conduct interviews / discussions at times and in places that are convenient and preserved confidentiality. Taking part in interviews / group discussions is expected to take less than 30-60 minutes and so should cause no more than minor inconvenience. Where interviews / group discussions are held online participants will have their data costs reimbursed in accordance with the existing KEMRI-Wellcome policy (1 GB of data; approximately Ksh. 250). Where interviews / group discussions are held face to face at people’s place of work no direct compensation will be provided but where appropriate participants will be offered refreshment (eg. a soda or cup of tea) if the interview is held duing a working break.

16.1 Risks

This study does not introduce risks to participants beyond those they would normally face in the context of illness or routine care, for example in the case of samples collected at ANCs. Sample collection from HCW, other frontline staff and HDSS residents will introduce risks associated with collection of blood samples and nasopharyngeal samples (HCW and other frontline staff only). Potential risks associated with collection of blood and nasopharyngeal samples include pain at the blood draw site and discomfort in the nasopharynges. These risks will be minimized by having sample collection conducted by competent staff trained in sample collection. For studies conducting RT-PCR testing, positive test results will be reported to the applicable County RRT. Individuals testing positive for SARS-CoV-2 by RT-PCR will be subject to national MoH guidelines, which may include isolation at designated facilities as well as tracing and quarantine of contacts, potentially at government-designated facilities. Isolation and quarantine at government-designated facilities maybe at the expense of individuals testing positive. Staff will be trained on how to respond to participants questions regarding positive SARS-CoV-2 results. There is some risk that additional follow-up visits after discharge could risk further spreading SARS-CoV-2 or introduce risk of SARS-CoV-2 infection if participants use public transport to attend follow-up visits. Such visits for participants enrolled in the clinical COVID-19 cohort may be converted to a phone call to obtain vital status, without sample collection, if the visit appears to be in conflict with Kenyan National Guidelines at any point during the study. Follow up visits for participants in the longitudinal serosurveillance of asymptomatic and symptomatic confirmed COVID-19 cases will be integrated within the MoH RRT COVID-19 home-based care program, minimizing the need to use public transport. There is a risk of breaching medical confidentiality. The principle of confidentiality and measures to protect confidential information will be part of staff training. Potential disadvantages for participants also include the time taken to attend follow ups and answer questions, and the potential for interviews to remind interviewees of difficult and disturbing incidents and situations in their lives. Training and standard SOPs will be implemented to help avoid these problems. Patients attending study follow-up visits at health facilities (CHAIN-COVID cohort) and HDSS residents attending the sample collection visit at a health facility will be have transport costs reimbursed (based on the distance traveled) and will be compensated for out of pocket expenses ranging from a minimum of KES 350 to a maximum of KES 650 per visit; this range is in line with KWTRP guidelines. Transferred healthcare workers or those invited back to the study health facilities for sample collection during their non-working hours will be reimbursed their actual transport costs and will receive KES 650 for out-of-pocket expenses.

Any potential risks from taking part in interviews / group discussions will be mitigated by preserving participants' confidentiality.

16.2 Benefits to patients and community as a whole

Hospitalized patients will benefit from institutional training, standardisation of procedures and additional staffing. Where health or social problems are identified, participants in inpatient surveillance will be referred to appropriate services. Findings

from this study are expected to lead to improvements in the national response to COVID-19 by generating novel data about disease incidence, prevalence of exposure, virus's effects on vulnerable populations, and the health systems challenges being faced by facilities mounting a response to the disease.

16.3 Confidentiality

Every effort will be taken to maintain normal medical confidentiality. All records and transcripts will be kept in a locked filing cabinet at the appropriate site, which is accessed only by the investigators and the study staff. For CIN-specific surveillance, all participant data will be deidentified. Health service assessment data will be facility level data but in instances where they represent a health worker response data will be de-identified (neither the name nor other personal identifiers collected). In the case of interviews / discussions all such data will only be linked to a unique code with a small number of named investigators having access to a file linking these codes to the respondents' details (eg. their age, profession, facility). For ANC surveillance, all included mothers will have a serial number assigned to them that will anonymise their associated data collection form and blood sample; there will be no document that links the samples to the mothers. At KWTRP-Kilifi, data from the clinical, laboratory and demographic surveillance will be stored in an integrated database Kilifi CGMR-C server. Data access and confidentiality will be overseen by the Manager, ICT department, and routine off site back-ups will be conducted to ensure data security. Additional confidentiality measures are detailed within the associated protocols. Only the investigators and the clinical monitor will have access to these records. Only de-identified data will be shared with the funder or other investigators, as specified under the section on data sharing.

16.4 Community engagement strategy

Community engagement will primarily be through the inpatient wards, OPDs and follow-up clinics at the hospital study sites and through the County Directors' offices. Study teams will also establish or leverage existing linkages with county and hospital health promotion teams to support dissemination of hospital, County of MoH COVID-19 educational materials. Sub-County Health Management Teams and health facility administrators will also be engaged. Partnerships with some County, Sub-County and health facilities stakeholders have already been established for sites that have ongoing clinical surveillance conducted under the protocols listed in Section 17 and these existing partnerships will be leveraged. Referral clinics and hospitals will be informed through these means. At this time further Community sensitisation appears inappropriate as it would break with national social distancing recommendations. The community engagement strategy will be revised should national recommendations be revised. We will consult with the KWTRP Community Engagement team to explore the feasibility and suitability of using non-contact mass communication strategies for engaging the community, such as radio announcements. When working with other organizations, we shall engage the community engagement teams at the respective organizations to identify appropriate strategies for engaging community members. At the Programme level, KWTRP has engaged and continues to engage community

members in collaboration with the Kilifi Department of Health through guest speaking roles at local Coastal region radio stations during which Programme researchers have covered a wide range of COVID-19 topics.

16.5 Stakeholder information giving

The key stakeholders in this study are the hospitals hosting the study, the community engaged in the research, the Ministry of Health, County Health Departments, the investigators and the funders. Written and oral (virtual/phone) information regarding the study's purpose, processes and findings will be given to each of these parties. The funders will be engaged through regular progress reports given by the scientific leads.

16.6 Individual informed consent

Individual informed consent will not be sought for the following activities: surveillance for suspected or confirmed COVID-19; ANC serosurveillance; retrospective serosurvey among hospitalized patients; and the analysis of trends in pneumonia and all-cause hospitalization and mortality within hospitalized adults at KCH. As described previously, the objective of ANC serosurveillance is population screening. There is no intention in providing individual test results to women. For this reason, routine identification data will not be collected. This is unlikely to cause any harm to the patients. The data to be collected includes age, parity, gravidity, gestational age and any new medical symptoms. Consent will be obtained from participating health facilities and the respective Counties to use the residual blood volumes to conduct public health surveillance of SARS-CoV-2. In the development of this protocol we request approval to publish the results of the population surveillance activities. The retrospective serosurvey will use stored samples from patients who consented to sample stored and future use under SSC 1433 (An effectiveness study in Kilifi District of 10-valent Pneumococcal Conjugate Vaccine administered through the routine childhood immunization programme). Through this protocol, we request approval to use these stored samples to assess for previous SARS-CoV-2 exposure in this population of patients without confirmed COVID-19. Pneumonia and all-cause admissions will be abstracted from the clinical surveillance database at KCH. Clinical and demographic characteristics are typically collected as part of KCH adult ward surveillance (SSC #1999).

Consent will be sought for long-term clinical follow-up of COVID-19 cases; investigation of suspected multisystem inflammatory syndrome; virological and serological surveillance of HCW and non-healthcare frontline staff; interviews / discussions with healthworkers, serological surveillance of HDSS residents, asymptomatic cases and symptomatic cases; as well as for host genetics studies. Studies involving individuals aged 13 to 17 years, inclusive, will seek written assent, in addition to parental consent. These studies will be carried out in conformity to the ICH-GCP principles for informed consent. These principles will be stated and explained clearly in an informed consent SOP. This will be the basis for training staff involved in obtaining informed consent. Patients, parents or guardians will receive an explanation of the study by a member of the study team in private and in an appropriate language (e.g., English, Kiswahili, Giryama or Dholuo). For hospitalized participants, consent will be obtained during the

stablisation period. They will be given a chance to ask questions before written consent for them, or their child, to be included in the study is sought. Potential participants needing time to consider participation will be allowed no less than 30 minutes but the time allowed may be longer for research activities where it is logistically feasible. In line with standard operating procedures, study staff will ask participants/ parents/ guardians questions to assess understanding. An impartial witness will be included in the event that the participant or parent/ guardian (for children) cannot read. Participants or their caregivers who are unable to write will be asked to provide a witnessed thumbprint. Written emergency assent will be obtained for patients severely ill at presentation to the health facility. As part of quality assurance, study documents will be reviewed to ensure that the applicable consent form is completed for each study participant. Participants/ parents/ guardians will be provided with a copy of the applicable signed consent document.

For interviews / discussions only professional healthworkers will be invited to participate. They will be provided with an information sheet about the purpose of data collection and the process. This will either be sent to them online or when a researcher is visiting their facility. They will be given time to read the information and ask any questions and then asked to give their permission / consent for the interview / group discussion as appropriate. Where the interview / discussion is being conducted online the respondents will be asked to send a structured email or message to the interviewer confirming they give permission / consent to take part and to have the interview / discussion recorded by the interviewer. At the start of the audio recording the particpants will be asked to confirm verbally that they have given their permission / consented to providing information as part of the research. Where interviews / discussions are conducted face-to-face then written informed consent will be obtained including for audio recording. Respondents will at any time be able to withdraw their permission / consent or ask for any information they have shared to be withdrawn from the study.

16.7 Training/ support for those involved in community engagement and administering consent

Virtual or in-person training in community engagement and consent will be given to all study staff prior to enrolment beginning. All persons administering consent with have research ethics and GCP training. Staff performing verbal autopsy will be trained in accordance with WHO recommendations by staff engaged with an existing verbal autopsy study. Recognizing that research managers, frontline researchers and field staff can face significant ethical dilemmas over the course of conducting their research, regular debriefs will be organized for staff to share any ethics dilemmas faced (85). These sessions will allow team members with different experience and expertise to share worries, carefully identify and explore any related ethical issues and researcher responsibilities, and agree on any appropriate action.

16.8 Feedback of information

Results of the study will be fed back to the study communities through each research institution's community representatives or community liaison group, public meetings (when government restrictions are eased), hospital and counties involved and the follow up clinics in each site, and nationally through the Emergency Operations Centre. Results will be shared through presentation at local and international scientific meetings as well as peer-reviewed publications.

16.9 Sample storage

Consent to participate will include permission to store samples for current research activities. Participants will indicate agreement to store samples for future research. Use of samples for future research will be contingent on ethical approval. Samples will be stored at the KWTRP biobank in Kilifi for the duration of the study. Access to the biobank is strictly controlled. After expiration of the storage period samples will be disposed of in accordance with the applicable institutional standard operating procedures for sample destruction.

16.10 Role of contributing studies

As described previously, the COVID-19 surveillance and epidemiologic evaluations described under this protocol will leverage data and/ or samples collected under other, SERU-approved protocols. The sections below summarize the scope of each contributing study and expected contributions to this protocol. The work described under this protocol will not subsume contributing studies as the scope of each of those studies extends beyond COVID-19 research.

16.10.1 SSC 3459: A Clinical Information Network – A technical collaboration with the Ministry of Health and county hospitals to support and improve strategies for audit, health service evaluation

Scope: To support: i) improved reporting to the Ministry of Health of routine morbidity, mortality and quality of care data from hospitals; ii) improved use of data to provide individual hospitals with regular reports on their morbidity, mortality and quality of care to promote quality improvement; iii) piloting the development of enhancements to local and national information systems to enable production of better health statistics; iv) and improved use of data for surveillance of mortality, morbidity and quality and for tracking the adoption of technologies and treatments recommended by the Ministry of Health across hospitals.

Contribution to SEECK protocol: Morbidity and mortality data specific to suspected and confirmed COVID-19 and health facility assessments from health facilities participating in the Clinical Information Network.

16.10.2 SSC 1433: An effectiveness study in Kilifi District of 10-valent pneumococcal conjugate vaccine administered through the routine childhood immunization programme

Scope: To evaluate: 1) the impact of pneumococcal conjugate vaccine (PCV) use on invasive pneumococcal disease (IPD) by monitoring all individuals in the Kilifi HDSS for

both immunization events and morbidity events; 2) impact of PCV use on pneumonia and all admissions to hospital; 3) the cost-effectiveness of PCV; 4) population immunity following vaccine introduction; 4) pneumococcal transmission patterns; and 5) molecular strain structure of pneumococcus.

Contribution to SEECK protocol: Clinical and laboratory data on hospitalized patients for assessment of trends in pneumonia and severe acute respiratory infection (SARI) hospitalization and mortality among patients admitted to Kilifi County Hospital. Stored samples for retrospective serosurvey.

16.10.3 SSC 1999: Description of the burden of disease in adults admitted to Kilifi District Hospital

Scope: To use routinely collected hospital and demographic data to determine the burden and rates of various clinical conditions in adults admitted to the medical wards at Kilifi District Hospital.

Contribution to SEECK protocol: Routinely collected hospital and demographic data for assessment of trends in pneumonia and all-cause hospitalization and in-hospital mortality among adults admitted to Kilifi County Hospital.

16.10.4 SSC 3420: Epidemiological and functional studies of candidate malaria-protective polymorphisms

Scope: To perform epidemiological and functional experimental studies with a view to gaining a better understanding of the manner in which malaria-protective polymorphisms affect the dynamics of the host-parasite interaction and prevent severe malaria episodes.

Contribution to SEECK protocol: Identification of polymorphisms in target genes of interest for use in analyses of the contribution of polymorphisms to COVID-19 susceptibility.

16.10.5 SSC 3257: The genetics of iron status and susceptibility to childhood infections

Scope: To assess whether: 1) iron deficiency and other micronutrients impair natural and vaccine-induced immunity thus increasing the risk of infections such as malaria and bacterial infections; and 2) early micronutrient deficiencies might be associated with cardiometabolic disease.

Contribution to SEECK protocol: Identification of polymorphisms in target genes of interest for use in analyses of the contribution of polymorphisms to COVID-19 susceptibility.

17 Expected application of findings

This study will rapidly deepen our understanding of COVID-19 incidence, exposure prevalence, how COVID-19 effects vulnerable population, the toll which the COVID-19 response has on the Kenyan healthcare system, potential role of host genetics and molecular mechanisms in the local context. This information may directly inform the

Kenyan and sub-Saharan African Response to SARS CoV-2. Secondly, it will identify the viability of SARS CoV-2 in faecal samples, which will inform how research laboratories should handle these samples during the pandemic, or during a future epidemic or endemic phase of this disease. This research will also provide data on the validity of antibody assays which will be informative for serological testing. This research will be vital to ensuring health science research after the pandemic is able to continue using faecal samples as a relatively low-risk, non-invasive sample type**.**

18 Budget

		KSH	USD
Personnel			
	Clinical surveillance	In-kind contribution	
	Virological and serological surveillance	95,560,215	1,005,897
	Host genetics studies	In-kind contribution	
	Molecular mechanisms studies	In-kind contribution	
Training and supervision			
	Clinical surveillance	758,400	6,895
	Virological and serological surveillance	176,016	1,853
	Host genetics studies	N/A	
	Molecular mechanisms studies	In-kind contribution	
Equipment			
	Clinical surveillance	In-kind contribution	
	Virological and serological surveillance	In-kind contribution	
	Host genetics studies	In-kind contribution	
	Molecular mechanisms studies	In-kind contribution	
Transportation			
	Clinical surveillance	N/A	
	Virological and serological surveillance	9,532,775	100,345
	Host genetics studies	1,425,000	15,000
	Molecular mechanisms studies	N/A	
Data collection - supplies and communication			
	Clinical surveillance	5,591,389	50,846
	Virological and serological surveillance	5,174,270	54,466
	Host genetics studies	In-kind contribution	
	Molecular mechanisms studies	In-kind contribution	
Data management and coordination			
	Clinical surveillance	812,897	7,390
	Virological and serological surveillance	N/A	

		KSH	USD
	Host genetics studies	500,000	5,263
	Molecular mechanisms studies	In-kind contribution	
Laboratory (supplies, sample collection, storage and testing)			
	Clinical surveillance	N/A	
	Dried blood spots cards and Mitra® devices	927,072	7,992
	Virological and serological surveillance	61,428,900	646,620
	Host genetics studies	5,225,000	55,000
	Molecular mechanisms studies	In-kind contribution	
PPE			
	Virological and serological surveillance	10,254,015	107,937
Sub-contracts			
	Clinical surveillance	N/A	
	Virological and serological surveillance	82,175,000	865,000
	Host genetics studies	N/A	
	Molecular mechanisms studies	N/A	
Sub-total		280,446,964	2,940,041
15% contingency		42,067,044	441,006
Total		322,514,008	3,381,047

18.1 Budget justification

The described research activities will leverage ongoing work and as such a substantial proportion of costs will be covered by in-kind contributions as described in the respective line budget items above. The budget will support personnel costs for investigators, fieldworkers, clinicians and support staff involved in recruitment of participants for virological/ serological surveillance studies, sample collection and analysis. The budget will also support training for staff involved in clinical and virological/ surveillance as well as supervision during conduct of study activities. Equipment needed for the current activities will leverage existing equipment and therefore no equipment is budgeted to be purchased. Transport costs will include costs associated with travel for staff to collect samples and sample shipping costs locally and internationally. Funding will be needed to support data collection, including provision of data (internet) bundles to participants in the qualitative exploration of challenges in health service provision, and management including printing paper forms, coordination of staff across the different study sites and collation/ management of data across the different study sites. The budget will further support purchase of sample collection supplies , RT-PCR testing, antibody assays and genetic testing as described for the

different studies. To minimize the risk of COVID-19 infection, personal protective equipment – as recommended by Programme/ MoH guidelines – will be purchased for staff. Serosurveillance of HDSS residents will involve collaboration with other HDSS outside Kilifi and costs for these independent HDSS will be covered under sub-contracts.

19 Timeline

Activity	Q2 2020	Q3 2020	Q4 2020	Q1 2021	Q2 2021
Protocol and tool development					
County engagement/introductions					
Ethical approval					
Clinical surveillance					
Health services assessments					
Serosurveillance among ANC clients					
Serosurveillance among HCW					
Serosurveillance among key frontline workers					
Serosurveillance among DSS residents					
Serosurveillance among asymptomatic cases					
Serosurveillance among asymptomatic cases					
Host genetics and molecular mechanisms studies					
Dissemination event					

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
2. World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
3. Johns Hopkins University Center for Systems Science and Engineering. COVID-19 Dashboard [Available from: https://coronavirus.jhu.edu/map.html.
4. Our World in Data. Coronavirus pandemic (COVID-19) – the data [Available from: https://ourworldindata.org/coronavirus-data.
5. Daily Nation. Tracking the coronavirus [Available from: https://www.nation.co.ke/newsplex/2718262-5496412-11gimflz/index.html.
6. World Health Organization (WHO). Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. 2020. Contract No.: WHO/2019-nCoV/Sci_Brief/Transmission_modes/2020.2.
7. Xiao F, Sun J, Xu Y, Li F, Huang X, Li H, et al. Infectious SARS-CoV-2 in Feces of Patient with Severe COVID-19. Emerg Infect Dis. 2020;26(8).
8. Ferretti L, Wymant C, Kendall M, Zhao L, Nurtay A, Abeler-Dörner L, et al. Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. Science. 2020;368(6491):eabb6936.
9. Brand SPC, Aziza R, Kombe IK, Agoti CN, Hilton J, Rock KS, et al. Forecasting the scale of the COVID-19 epidemic in Kenya. medRxiv. 2020:2020.04.09.20059865.
10. National Institude for Communicable Diseases. Clinical management of suspected or confirmed COVID-19 disease - Version 4 (18thMay2020) [Available from: https://www.nicd.ac.za/wp-content/uploads/2020/05/Clinical-management-of-suspected-or-confirmed-COVID-19-Version-4.pdf.
11. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill. 2020;25(10).
12. Ministry of Health. COVID-19 Outbreak in Kenya Daily Situation Report – 050. Nairobi: Government of Kenya; 2020 7th May 2020.
13. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497-506.
14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
15. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. 2020.
16. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.

17. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42.
18. Fu L, Fei J, Xiang H-X, Xiang Y, Tan Z-X, Li M-D, et al. Analysis of Death Risk Factors Among 200 COVID-19 Patients in Wuhan, China: A Hospital-Based Case-Cohort Study 2020 [Available from: https://ssrn.com/abstract=3551430 or http://dx.doi.org/10.2139/ssrn.3551430
19. Mahase E. Covid-19: concerns grow over inflammatory syndrome emerging in children. BMJ. 2020;369:m1710.
20. World Health Organization (WHO). Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 2020 [Available from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19.
21. World Health Organization (WHO). "Solidarity" clinical trial for COVID-19 treatments [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments.
22. MORU Tropical Health Network. COPCOV trial [Available from: https://www.tropmedres.ac/covid-19/copcov.
23. World Health Organization (WHO). Draft landscape of COVID-19 candidate vaccines (2 June 2020) [Available from: https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines.
24. Parohan M, Yaghoubi S, Seraj A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality of adult inpatients with Coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of retrospective studies. medRxiv. 2020:2020.04.09.20056291.
25. van Gemert F, Kirenga B, Chavannes N, Kamya M, Luzige S, Musinguzi P, et al. Prevalence of chronic obstructive pulmonary disease and associated risk factors in Uganda (FRESH AIR Uganda): a prospective cross-sectional observational study. The Lancet Global Health. 2015;3(1):e44-e51.
26. Salvi S. The silent epidemic of COPD in Africa. The Lancet Global Health. 2015;3(1):e6-e7.
27. Chisti MJ, Tebruegge M, La Vincente S, Graham SM, Duke T. Pneumonia in severely malnourished children in developing countries - mortality risk, aetiology and validity of WHO clinical signs: a systematic review. Trop Med Int Health. 2009;14(10):1173-89.
28. Gallagher KE, Knoll MD, Prosperi C, Baggett HC, Brooks WA, Feikin DR, et al. The Predictive Performance of a Pneumonia Severity Score in Human Immunodeficiency Virus–negative Children Presenting to Hospital in 7 Low- and Middle-income Countries. Clinical Infectious Diseases. 2019;70(6):1050-7.
29. Shah A, Frost JN, Aaron L, Donovan K, Drakesmith H, McKechnie SR, et al. Systemic hypoferremia and severity of hypoxemic respiratory failure in COVID-19. Critical Care. 2020;24(1):320.
30. Jayaweera J, Reyes M, Joseph A. Childhood iron deficiency anemia leads to recurrent respiratory tract infections and gastroenteritis. Sci Rep. 2019;9(1):12637.

31. Taneri PE, Gómez-Ochoa SA, Llanaj E, Raguindin PF, Rojas LZ, Roa-Díaz ZM, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. Eur J Epidemiol. 2020;35(8):763-73.
32. Mitchell F. Vitamin-D and COVID-19: do deficient risk a poorer outcome? Lancet Diabetes Endocrinol. 2020;8(7):570.
33. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr Rev. 2019;40(4):1109-51.
34. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. Bmj. 2017;356:i6583.
35. D'Avolio A, Avataneo V, Manca A, Cusato J, De Nicolò A, Lucchini R, et al. 25-Hydroxyvitamin D Concentrations Are Lower in Patients with Positive PCR for SARS-CoV-2. Nutrients. 2020;12(5).
36. Castillo ME, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, Miranda JL, Bouillon R, et al. "Effect of Calcifediol Treatment and best Available Therapy versus best Available Therapy on Intensive Care Unit Admission and Mortality Among Patients Hospitalized for COVID-19: A Pilot Randomized Clinical study". J Steroid Biochem Mol Biol. 2020:105751.
37. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med. 2020;382(12):1177-9.
38. Long Q-x, Deng H-j, Chen J, Hu J, Liu B-z, Liao P, et al. Antibody responses to SARS-CoV-2 in COVID-19 patients: the perspective application of serological tests in clinical practice. medRxiv. 2020:2020.03.18.20038018.
39. Okba NMA, Muller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. SARS-CoV-2 specific antibody responses in COVID-19 patients. medRxiv. 2020:2020.03.18.20038059.
40. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020.
41. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clinical Infectious Diseases. 2020.
42. Scott JAG, Fine P. Review of international seroepidemiological studies of SARS-CoV-2 (25th May 2020). 2020.
43. Uyoga S, Adetifa IMO, Karanja HK, Nyagwange J, Tuju J, Wanjiku P, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Kenyan blood donors. medRxiv. 2020:2020.07.27.20162693.
44. Winter AK, Hegde ST. The important role of serology for COVID-19 control. Lancet Infect Dis. 2020.
45. Miller LH, Mason SJ, Clyde DF, McGinniss MH. The resistance factor to Plasmodium vivax in blacks. The Duffy-blood-group genotype, FyFy. N Engl J Med. 1976;295(6):302-4.

46. Ciancanelli MJ, Huang SX, Luthra P, Garner H, Itan Y, Volpi S, et al. Infectious disease. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. Science. 2015;348(6233):448-53.
47. Hernandez N, Melki I, Jing H, Habib T, Huang SSY, Danielson J, et al. Life-threatening influenza pneumonitis in a child with inherited IRF9 deficiency. J Exp Med. 2018;215(10):2567-85.
48. Lim HK, Huang SXL, Chen J, Kerner G, Gilliaux O, Bastard P, et al. Severe influenza pneumonitis in children with inherited TLR3 deficiency. J Exp Med. 2019;216(9):2038-56.
49. Lamborn IT, Jing H, Zhang Y, Drutman SB, Abbott JK, Munir S, et al. Recurrent rhinovirus infections in a child with inherited MDA5 deficiency. J Exp Med. 2017;214(7):1949-72.
50. Asgari S, Schlapbach LJ, Anchisi S, Hammer C, Bartha I, Junier T, et al. Severe viral respiratory infections in children with IFIH1 loss-of-function mutations. Proc Natl Acad Sci U S A. 2017;114(31):8342-7.
51. Zhang SY, Jouanguy E, Ugolini S, Smahi A, Elain G, Romero P, et al. TLR3 deficiency in patients with herpes simplex encephalitis. Science. 2007;317(5844):1522-7.
52. Pérez de Diego R, Sancho-Shimizu V, Lorenzo L, Puel A, Plancoulaine S, Picard C, et al. Human TRAF3 adaptor molecule deficiency leads to impaired Toll-like receptor 3 response and susceptibility to herpes simplex encephalitis. Immunity. 2010;33(3):400-11.
53. Andersen LL, Mørk N, Reinert LS, Kofod-Olsen E, Narita R, Jørgensen SE, et al. Functional IRF3 deficiency in a patient with herpes simplex encephalitis. J Exp Med. 2015;212(9):1371-9.
54. Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, et al. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. Science. 1996;273(5283):1856-62.
55. Liu R, Paxton WA, Choe S, Ceradini D, Martin SR, Horuk R, et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. Cell. 1996;86(3):367-77.
56. Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, et al. Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature. 1996;382(6593):722-5.
57. Li W, Zhang C, Sui J, Kuhn JH, Moore MJ, Luo S, et al. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. Embo j. 2005;24(8):1634-43.
58. Kuo CL, Pilling LC, Atkins JL, Masoli JAH, Delgado J, Kuchel GA, et al. APOE e4 genotype predicts severe COVID-19 in the UK Biobank community cohort. J Gerontol A Biol Sci Med Sci. 2020.
59. Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, et al. Relationship between the ABO Blood Group and the COVID-19 Susceptibility. medRxiv. 2020:2020.03.11.20031096.
60. Zietz M, Tatonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. medRxiv. 2020:2020.04.08.20058073.

61. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis. medRxiv. 2020:2020.05.31.20114991.
62. Vuille-dit-Bille RN, Camargo SM, Emmenegger L, Sasse T, Kummer E, Jando J, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. Amino Acids. 2015;47(4):693-705.
63. Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. Pharmacol Ther. 2010;128(1):119-28.
64. Wein AN, McMaster SR, Takamura S, Dunbar PR, Cartwright EK, Hayward SL, et al. CXCR6 regulates localization of tissue-resident memory CD8 T cells to the airways. J Exp Med. 2019;216(12):2748-62.
65. Bugbank. Critical evaluation of the rs2076205 association with COVID-19 susceptibility in UK Biobank [Available from: https://news.bugbank.uk/2020/05/critical-evaluation-of-rs2076205.html.
66. Woodard-Grice AV, Lucisano AC, Byrd JB, Stone ER, Simmons WH, Brown NJ. Sex-dependent and race-dependent association of XPNPEP2 C-2399A polymorphism with angiotensin-converting enzyme inhibitor-associated angioedema. Pharmacogenet Genomics. 2010;20(9):532-6.
67. Duan QL, Nikpoor B, Dube MP, Molinaro G, Meijer IA, Dion P, et al. A variant in XPNPEP2 is associated with angioedema induced by angiotensin I-converting enzyme inhibitors. Am J Hum Genet. 2005;77(4):617-26.
68. Parpia AS, Ndeffo-Mbah ML, Wenzel NS, Galvani AP. Effects of Response to 2014-2015 Ebola Outbreak on Deaths from Malaria, HIV/AIDS, and Tuberculosis, West Africa. Emerg Infect Dis. 2016;22(3):433-41.
69. Delamou A, Ayadi AME, Sidibe S, Delvaux T, Camara BS, Sandouno SD, et al. Effect of Ebola virus disease on maternal and child health services in Guinea: a retrospective observational cohort study. Lancet Glob Health. 2017;5(4):e448-e57.
70. Elston JW, Cartwright C, Ndumbi P, Wright J. The health impact of the 2014-15 Ebola outbreak. Public Health. 2017;143:60-70.
71. Ojal J, Brand SP, Were V, Okiro EA, Kombe IK, Mburu C, et al. Revealing the extent of the COVID-19 pandemic in Kenya based on serological and PCR-test data. medRxiv. 2020:2020.09.02.20186817.
72. Neotrexy. Mitra Cartridge Dried Blood Spot Collection Capillary Blood Sampling Device. In: Corp N, editor. Torrance Califonia2022.
73. Kenya Ministry of Health. Case definition for novel coronavirus disease (COVID-19) V25032020 [Available from: http://www.health.go.ke/wp-content/uploads/2020/04/COVID-19-Case-Definition-25-March-2020.pdf.
74. Alegana VA, Khazenzi C, Akech SO, Snow RW. Estimating hospital catchments from in-patient admission records: a spatial statistical approach applied to malaria. Sci Rep. 2020;10(1):1324.
75. Marty FM, Chen K, Verrill KA. How to Obtain a Nasopharyngeal Swab Specimen. New England Journal of Medicine. 2020.

76. Scott JA, Bauni E, Moisi JC, Ojal J, Gatakaa H, Nyundo C, et al. Profile: The Kilifi Health and Demographic Surveillance System (KHDSS). Int J Epidemiol. 2012;41(3):650-7.
77. Odhiambo FO, Laserson KF, Sewe M, Hamel MJ, Feikin DR, Adazu K, et al. Profile: the KEMRI/CDC Health and Demographic Surveillance System--Western Kenya. Int J Epidemiol. 2012;41(4):977-87.
78. Beguy D, Elung'ata P, Mberu B, Oduor C, Wamukoya M, Nganyi B, et al. Health & Demographic Surveillance System Profile: The Nairobi Urban Health and Demographic Surveillance System (NUHDSS). Int J Epidemiol. 2015;44(2):462-71.
79. World Health O. Population-based age-stratified seroepidemiological investigation protocol for coronavirus 2019 (COVID-19) infection, 26 May 2020. Geneva: World Health Organization; 2020 2020. Contract No.: WHO/2019-nCoV/Seroepidemiology/2020.2.
80. Skol AD, Scott LJ, Abecasis GR, Boehnke M. Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies. Nat Genet. 2006;38(2):209-13.
81. Shabalin AA. Matrix eQTL: ultra fast eQTL analysis via large matrix operations. Bioinformatics. 2012;28(10):1353-8.
82. Sande CJ, Mutunga M, Muteti J, Berkley JA, Nokes DJ, Njunge J. Untargeted analysis of the airway proteomes of children with respiratory infections using mass spectrometry based proteomics. Sci Rep. 2018;8(1):13814.
83. Sande CJ, Njunge JM, Mwongeli Ngoi J, Mutunga MN, Chege T, Gicheru ET, et al. Airway response to respiratory syncytial virus has incidental antibacterial effects. Nat Commun. 2019;10(1):2218.
84. Sande CJ, Waeni JM, Njunge JM, Mutunga MN, Gicheru E, Kibinge NK, et al. In-silico immune cell deconvolution of the airway proteomes of infants with pneumonia reveals a link between reduced airway eosinophils and an increased risk of mortality. bioRxiv. 2020:840090.
85. Molyneux S, Marsh V. Commentary 1: Sharing and Responding to Day-to-Day Ethics Challenges in Health Research. J Empir Res Hum Res Ethics. 2019;14(5):513-5.

20 Appendices

20.1 Appendix 1 – Lead investigators by objective

	Description	Lead	Comments
Primary objective	To estimate the burden of COVID-19 and prevalence of exposure to SARS-CoV-2		
	• Incidence of suspected and confirmed COVID-19 in hospitalized children and adults	Dr Ambrose Agweyu	Associated protocol: SSC 3459
	• Cumulative incidence of confirmed COVID-19 and seroepidemiology of SARS-CoV-2 antibodies in HCW	Dr Anthony Etyang	
	• Seroepidemiology of SARS-CoV-2 antibodies in ANC clients	Dr Katherine Gallagher	
	• Seroepidemiology of SARS-CoV-2 antibodies in non-healthcare frontline staff	Dr Wangeci Kagucia & Prof Anthony Scott	
	• Seroepidemiology of SARS-CoV-2 antibodies in HDSS residents	Dr Ifedayo Adetifa	
	• Seroepidemiology of SARS-CoV-2 antibodies in asymptomatic PCR-confirmed cases	Dr Ambrose Agweyu	
	• Seroepidemiology of SARS-CoV-2 antibodies in symptomatic PCR-confirmed cases	Dr Geofrey Omuse & Dr Daniel Maina	
	• Retrospective SARS-CoV-2 serosurvey among hospitalized patients	Prof Anthony Scott & Prof George Warimwe	Associated protocol: SSC 1433
Secondary objective #1	To describe the clinical presentation, course and outcomes - including risk factors – in all and highly vulnerable adults and children, such as those with HIV, chronic non-communicable diseases and malnutrition; determine the quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2 in hospitalized COVID-19 patients		
	• Clinical presentation, course and outcomes in all children and adults	Dr Ambrose Agweyu	Associated protocols: SSC 3459; SSC 1999

	Description	Lead	Comments
	• Clinical presentation, course and outcomes in highly vulnerable adults and children	Prof Jay Berkeley	Associated protocol: SSC 3459
	• Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2 in hospitalized patients	Prof Jay Berkeley	Associated protocol: SSC 3459
Secondary objective #2	To describe and compare trends in hospitalization and mortality due to all causes and pneumonia in adults and children	Mr Mark Otiende & Prof Anthony Scott	Associated protocols: SSC 1433 and SSC 1999
Secondary objective #3	To examine utilization of respiratory care interventions, up-referral, down-referral, criteria for discharge and determine the impact of local SARS-CoV-2 response on the ability of the Kenyan health system to continue to deliver other health services, including management of acute illness (diarrhea, pneumonia, malaria, HIV), nutritional rehabilitation, follow-up care, prevention of mother to child HIV infection, and immunization services	Dr Jalemba Aluvaala & Prof Mike English & Dr. Jacquie Oliwa	Associated protocol: SSC 3459
Secondary objective #4	To investigate host genetic determinants of susceptibility to COVID-19, and molecular mechanisms of SARS-CoV-2 severity and death in hospitalized adults with long-term biomass exposure and severe undernutrition		
	• Host-genetic determinants	Dr Silvia N. Kariuki & Dr Sarah Atkinson	Associated protocols: SSC 3420 and SSC 3257
	• Molecular mechanisms	Dr Charles Sande	

20.2 Appendix 2 – Investigator roles

	Clinical epidemiology of suspected and confirmed COVID-19 in hospitalized patients	**Clinical presentation, course and outcome of COVID-19 in vulnerable groups**	**Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2**	**Trends in adult pneumonia and all-cause admissions and mortality, KCH**	**Health services assessments**	**Virological and serological surveillance in HCW**	**Virological and serological surveillance in other frontline staff**	**Serological surveillance in ANC clients**	**Serolgoical surveillance in HDSS residents**	**Serolgoical surveillance in asymptomatic PCR-confirmed cases**	**Serolgoical surveillance in symptomatic PCR-confirmed cases**	**Retrospective serosurvey among hospitalized patients**	**Host-genetics**	**Molecular mechanisms**	**Antibody assays**
A Abdi – Molecular biologist						X[c,d,e]	X[c,d,e]	X[c,d,e]	X[c,d,e]	X[c,d,e]	X[c,d,e]				
I Adetifa – Clinical epidemiologist	X[b,d]			X[d]		X[d]	X[d]	X[d]	X[***a,b,d,e**]	X[d]	X[d]				
A Agweyu – Head, Epidemiology & Demography, KWTRP	X[*** a,b,d,e**]	X[b]	X[b]	X[b]	X[**a,b,d,e**]	X[b,d]	X[b,d]	X[b,d]	X[b,d]	X[* a,b,d,e]	X[b,d]	X[a,d,e]	X[b]	X[b]	X[b]
D Akech – Assistant Research Officer							X[b]		X[b,c]						
S Akech – Clinical epidemiologist	X[**a,b,d,e**]				X[**a,b,d,e**]										
V Akelo – Clinical epidemiologist									X[a,b,d,e]						
V Alegana - Epidemiologist	X[**a,b,d,e**]														

	Clinical epidemiology of suspected and confirmed COVID-19 in hospitalized patients	Clinical presentation, course and outcome of COVID-19 in vulnerable groups	Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2	Trends in adult pneumonia and all-cause admissions and mortality, KCH	Health services assessments	Virological and serological surveillance in HCW	Virological and serological surveillance in other frontline staff	Serological surveillance in ANC clients	Serolgoical surveillance in HDSS residents	Serolgoical surveillance in asymptomatic PCR-confirmed cases	Serolgoical surveillance in symptomatic PCR-confirmed cases	Retrospective serosurvey among hospitalized patients	Host-genetics	Molecular mechanisms	Antibody assays
J Aluvaala – Clinical epidemiologist	X[b,d,e]	X[b,d,e]	X[b,d,e]		X*[a,b,d,e]										
R Aman – Chief Administrative Secretary, MoH	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]		X[b]	X[b]	X[b]
S Atkinson – Genetic epidemiologist													X*[a,b,d,e]		
BAT Barr – Director, Western Kenya CDC									X[a,b,d,e]						
E Barasa – Nairobi Director, KWTRP					X **[a,b,d,e]**										
H Barsosio – Clinical Epidemiologist						X[b,d,e]		X[b,d,e]							
P Bejon – Executive Director KWTRP															X **[a,b,d,e]**
J Berkley – Clinical epidemiologist	X[a,b,d,e]	X*[a,b,d,e]	X*[a,b,d,e]		X **[a,b,d,e]**								X[a,b,d,e]		

	Clinical epidemiology of suspected and confirmed COVID-19 in hospitalized patients	Clinical presentation, course and outcome of COVID-19 in vulnerable groups	Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2	Trends in adult pneumonia and all-cause admissions and mortality, KCH	Health services assessments	Virological and serological surveillance in HCW	Virological and serological surveillance in other frontline staff	Serological surveillance in ANC clients	Serolgoical surveillance in HDSS residents	Serolgoical surveillance in asymptomatic PCR-confirmed cases	Serolgoical surveillance in symptomatic PCR-confirmed cases	Retrospective serosurvey among hospitalized patients	Host-genetics	Molecular mechanisms	Antibody assays
M Chepkirui – Data Scientist	X **a,b,d,e**				X **b,d,e**										
M English – Health Systems Researcher	X **a,b,d,e**	X a,b,d,e	X a,b,d,e		X **a,b,d,e**										
A Etyang – Clinical epidemiologist	X b	X b		X b,d,e		X* a,b,d,e	X d	X d	X d	X d	X d		X a,b,d,e		
K Gallagher – Epidemiologist						X a,d,e	X d	X a,b,d,e*	X d,e	X d	X d				
D Gathara – Clinical epidemiologist	X **a,b,d,e**				X **a,b,d,e**										
E Gicheru – Immunology technician														X b,c	
G Githinji – Bioinformatician						X c	X c								
M Hamaluba – Head, Clinical Research						X **a,b,d,e**									
G Irimu – Health Services Researcher	X **a,b,d,e**				X **a,b,d,e**										

	Clinical epidemiology of suspected and confirmed COVID-19 in hospitalized patients	Clinical presentation, course and outcome of COVID-19 in vulnerable groups	Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2	Trends in adult pneumonia and all-cause admissions and mortality, KCH	Health services assessments	Virological and serological surveillance in HCW	Virological and serological surveillance in other frontline staff	Serological surveillance in ANC clients	Serolgoical surveillance in HDSS residents	Serolgoical surveillance in asymptomatic PCR-confirmed cases	Serolgoical surveillance in symptomatic PCR-confirmed cases	Retrospective serosurvey among hospitalized patients	Host-genetics	Molecular mechanisms	Antibody assays
L Isaaka – Research Medical Officer	X **a,b,d,e**														
C Kalu – Assistant Research Officer							X b,d,e								
D Kamuya – Head, HSRE KWTRP					X **a,b,d,e**										
E Kagucia - Epidemiologist	X b,d	X b	X b	X a,d,e	X b	X d	X ***a,b,d,e**	X b	X b,d,e	X b,d,e	X b,d,e	X a,b,d,e	X b	X b	X b
A Karani – Microbiologist						X c	X c	X c	X c			X c			
H Karanja – Biomedical Laboratory Scientist						X c	X c	X c	X c	X c	X c	X c			X c,d,e
SN Kariuki – Molecular epidemiologist													X *a,b,c,d,e		
S Kariuki – Chief Research Officer						X b,d,e									
K Kasera – Head, EOC	X b	X b	X b	X b	X b	X b	X b	X b	X b	X b	X b				
M. Kimani – Clinical epidemiologist									X a,b,e						

	Clinical epidemiology of suspected and confirmed COVID-19 in hospitalized patients	Clinical presentation, course and outcome of COVID-19 in vulnerable groups	Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2	Trends in adult pneumonia and all-cause admissions and mortality, KCH	Health services assessments	Virological and serological surveillance in HCW	Virological and serological surveillance in other frontline staff	Serological surveillance in ANC clients	Serolgoical surveillance in HDSS residents	Serolgoical surveillance in asymptomatic PCR-confirmed cases	Serolgoical surveillance in symptomatic PCR-confirmed cases	Retrospective serosurvey among hospitalized patients	Host-genetics	Molecular mechanisms	Antibody assays
S Kinyanjui – Head, Training KWTRP															X[b,d,e]
F ter Kuile – Clinical epidemiologist						X[b,d,e]									
N Kuya – Clinical Officer							X[b,d,e]								
R Lucinde – Research Medical Officer						X[a,b,d,e]		X[a,b,e]	X[b,e]						
D Maina – Clinical pathologist											X[a-e]				
C Mburu – Mathematical modeler									X[d,e]						
N Mturi – Head, Clinical Services KWTRP	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]									
M Munene – Research Governance Manager	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]		X[b]	X[b]	X[b]
M Mwangangi – CAS MoH	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]				
J Mwaniki – Medical microbiologist	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]												

	Clinical epidemiology of suspected and confirmed COVID-19 in hospitalized patients	Clinical presentation, course and outcome of COVID-19 in vulnerable groups	Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2	Trends in adult pneumonia and all-cause admissions and mortality, KCH	Health services assessments	Virological and serological surveillance in HCW	Virological and serological surveillance in other frontline staff	Serological surveillance in ANC clients	Serolgoical surveillance in HDSS residents	Serolgoical surveillance in asymptomatic PCR-confirmed cases	Serolgoical surveillance in symptomatic PCR-confirmed cases	Retrospective serosurvey among hospitalized patients	Host-genetics	Molecular mechanisms	Antibody assays
E Nduati – Molecular biologist						X[c,d,e]	X[c,d,e]	X[c,d,e]	X[c,d,e]	X[c,d,e]	X[c,d,e]				
R Ndung'u														X[a,b,c,d,e]	
F Ndungu - Immunologist						X[c,d,e]	X[c,d,e]	X[c,d,e]	X[c,d,e]	X[c,d,e]	X[c,d,e]				
M Ng'oda – Research Officer									X[b,c]						
A. Ng'ong'a						X[b,d,e]									
W Ng'ang'a – Technical advisor, Office of the President	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]				
J Njunge – Protein scientist														X[a,b,c,d,e]	
J Nokes - Epidemiologist						X[e]	X[e]	X[e]	X[e]						
A Nyaguara – Head, Surveillance KWTRP	X[b,d]	X[b]		X[b]					X[b]						
J Nyagwange – Molecular biologist						X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]			X[c,d,e]

	Clinical epidemiology of suspected and confirmed COVID-19 in hospitalized patients	Clinical presentation, course and outcome of COVID-19 in vulnerable groups	Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2	Trends in adult pneumonia and all-cause admissions and mortality, KCH	Health services assessments	Virological and serological surveillance in HCW	Virological and serological surveillance in other frontline staff	Serological surveillance in ANC clients	Serolgoical surveillance in HDSS residents	Serolgoical surveillance in asymptomatic PCR-confirmed cases	Serolgoical surveillance in symptomatic PCR-confirmed cases	Retrospective serosurvey among hospitalized patients	Host-genetics	Molecular mechanisms	Antibody assays
C Nyaigoti – Epidemiologist						X[c]	X[c]								
B Nyamwaya – Research Medical Officer	X[b,d]	X[b]		X[b]					X[b,e]						
J Nyiro - Epidemiologist						X[c]	X[c]								
D Obor – HDSS coordinator									X[b,d,e]						
B Ochieng – Research Officer							X[b,d,e]								
E Ochomo – Medical Entomologist							X[b,d,e]								
M Ogero - Statistician	X[a,b,d,e]				X[a,b,d,e]										
J Ojal – Mathematical modeler						X[d,e]	X[d,e]	X[d,e]	X[d,e]						
E Okiro - Epidemiologist	X[a,b,d,e]				X[a,b,d,e]										
J Oliwa – Health Systems Researcher	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]		X[a,b,d,e]										

	Clinical epidemiology of suspected and confirmed COVID-19 in hospitalized patients	Clinical presentation, course and outcome of COVID-19 in vulnerable groups	Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2	Trends in adult pneumonia and all-cause admissions and mortality, KCH	Health services assessments	Virological and serological surveillance in HCW	Virological and serological surveillance in other frontline staff	Serological surveillance in ANC clients	Serolgoical surveillance in HDSS residents	Serolgoical surveillance in asymptomatic PCR-confirmed cases	Serolgoical surveillance in symptomatic PCR-confirmed cases	Retrospective serosurvey among hospitalized patients	Host-genetics	Molecular mechanisms	Antibody assays
G Omuse – Clinical pathologist											X[a-e]				
D Onyango – Medical epidemiologist									X[b,d,e]						
M Otiende - Epidemiologist	X[b,d]			X*[a,b,d,e]											
I Otiti – Medical doctor						X[b,d,e]									
I Oyier – Head, Biosciences KWTRP						X[c]	X[c]	X[c]	X[c]				X[a,b,c,d,e]		X[c]
M Rono – Molecular biologist													X[a,b,c,d,e]		
C Sande – Immunoepidemiologist														X[a,b,c,d,e]	
A Scott – Clinical epidemiologist	X[d]			X*[a,d,e]		X[a,d,e]	X*[a,d,e]	X[a,d,e]	X[a,d,e]			X*[a,b,d,e]			
R Shah – Infectious disease physician											X[b,d,e]				
A Sigilai – Assistant Research Officer									X[b,c]						

	Clinical epidemiology of suspected and confirmed COVID-19 in hospitalized patients	Clinical presentation, course and outcome of COVID-19 in vulnerable groups	Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2	Trends in adult pneumonia and all-cause admissions and mortality, KCH	Health services assessments	Virological and serological surveillance in HCW	Virological and serological surveillance in other frontline staff	Serological surveillance in ANC clients	Serological surveillance in HDSS residents	Serolgoical surveillance in asymptomatic PCR-confirmed cases	Serolgoical surveillance in symptomatic PCR-confirmed cases	Retrospective serosurvey among hospitalized patients	Host-genetics	Molecular mechanisms	Antibody assays
B Singa – Clinical Epidemiologist	X[a,b,d,e]	X*[a,b,d,e]	X*[a,b,d,e]		X [a,b,d,e]								X[a,b,d,e]		
R Snow - Epidemiologist	X[a,b,d,e]														
K Tickell – Clinical epidemiologist		X[a,d,e]	X[a,d,e]												
C Tigoi – Microbiologist	X[a,b,d,e]	X[a,b,d,e]	X[a,b,d,e]												
B Tsofa – Centre Director, KEMRI-CGMR,C					X[a,b,d,e]										
J Tuju – Molecular biologist						X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]			X[c,d,e]
S Uyoga – Molecular epidemiologist						X[d]	X[d]	X[d]	X[d]	X[d]	X[d]				
S Voller – Programme Manager						X[b]	X[b]	X[b]	X[b]	X[b]	X[b]				
J Waeni - Bioinformatician														X[a,b,c,d,e]	
J Walson – Clinical Epidemiologist	X[a,b,d,e]	X [a,b,d,e]	X [a,b,d,e]		X [a,b,d,e]								X[a,b,d,e]		
G Warimwe - Vaccinologist						X[c]	X[c]	X[c]	X[c]			X*[a-e]			X*[a,b,c,d,e]

	Clinical epidemiology of suspected and confirmed COVID-19 in hospitalized patients	Clinical presentation, course and outcome of COVID-19 in vulnerable groups	Quantity, duration and contribution to transmission of faecal shedding of SARS-CoV-2	Trends in adult pneumonia and all-cause admissions and mortality, KCH	Health services assessments	Virological and serological surveillance in HCW	Virological and serological surveillance in other frontline staff	Serological surveillance in ANC clients	Serolgoical surveillance in HDSS residents	Serolgoical surveillance in asymptomatic PCR-confirmed cases	Serolgoical surveillance in symptomatic PCR-confirmed cases	Retrospective serosurvey among hospitalized patients	Host-genetics	Molecular mechanisms	Antibody assays
F Wekesah - Epidemiologist									X[b,d,e]						
T Williams – Genetic epidemiologist													X[a,b,d,e]		
A Ziraba – Clinical epidemiologist									X[b,d,e]						

*= Lead investigator

[a]= Study design; [b]= Data acquisition/ Coordination/ Supervision; [c]= Sample processing/ testing; [d]= Analysis; [e]= Report/ manuscript writing

ANC= Antenatal clinic; CAS= Chief Administrative Secretary; EOC = Emergency Operations Centre; KCH= Kilifi County Hospital; KEMRI= Kenya Medical Research Institute; HCW= Healthcare workers; HDSS= Health and Demographic Surveillance System; HSRE= Health Services and Research Ethics; MoH= Ministry of Health

20.3 Participant information sheets and consent forms (enclosed)

20.3.1 Clinical surveillance

(1) CHAIN-COVID Paediatric Ward Consent Form, version 1.1
(2) CHAIN-COVID Paediatric Ward Assent Form, version 1.1
(3) CHAIN-COVID Paediatric Ward Emergency Assent Form, version 1.1
(4) CHAIN-COVID Adult Ward Consent Form, version 1.1
(5) CHAIN-COVID Adult Ward Assent Form, version 1.1
(6) CHAIN-COVID Adult Ward Emergency Assent Form, version 1.1

20.3.2 Serological surveillance

(1) SARS-CoV-2 Serosurveillance Studies among Healthcare Workers in Kenya Consent Form, version 1.3
(2) SARS-CoV-2 Serosurveillance Studies among Frontline Workers in Kenya Consent Form, version 1.2
(3) SARS-CoV-2 Serosurveillance Studies among Health and Demographic Surveillance System Residents in Kenya Consent Form, version 2.2
(4) SARS-CoV-2 Serosurveillance Studies among Health and Demographic Surveillance System Residents in Kenya Assent Form, version 2.2
(5) Seroepidemiology of Asymptomatic, PCR-confirmed SARS-CoV-2 Cases Consent Form, version 1.1
(6) Seroepidemiology of Asymptomatic, PCR-confirmed SARS-CoV-2 Cases Assent Form, version 1.1
(7) Seroepidemiology of Symptomatic, PCR-confirmed SARS-CoV-2 Cases Consent Form, version 1.1
(8) Seroepidemiology of Symptomatic, PCR-confirmed SARS-CoV-2 Cases Assent Form, version 1.1

20.3.3 Health services assessments

(1) Qualitative exploration of the challenges facilities face in providing COVID-19 and routine services – Information sheet and consent form

20.4 Data collection forms (enclosed)

(1) COVID-19 Hospital-based Sentinel Surveillance Case Investigation Form
(2) Healthcare worker serosurveillance data collection form
(3) Non-healthcare frontline worker serosurveillance data collection form
(4) ANC serosurveillance data collection form
(5) HDSS serosurveillance data collection form
(6) Asymptomatic serosurveillance data collection form
(7) Qualitative exploration of the challenges facilities face in providing COVID-19 and routine services – Individual interview / group discussion guide