Rethinking the Evidence on COVID in Africa

Authors

Philip Bejon[1,2], Ambrose Agweyu[1,3], Isabella Oyier[1], Mainga Hamaluba[1], Dorcas Kamuya[1], Sam Kinyanjui[1,2], Edwine Barasa[1,2]

Affiliations

1. KEMRI-Wellcome Trust Research Programme, Centre for Geographical Medicine Research (Coast), Kenya

2. Modernising Medical Microbiology, Nuffield Dept of Medicine, University of Oxford, UK

3. Centre for Tropical Medicine and Global Health, Nuffield Dept of Medicine, University of Oxford, UK

4. London School of Hygiene and Tropical Medicine, London, UK

Abstract

The COVID pandemic was predicted to cause substantial mortality in Africa. However, experiences from many countries in Africa were notable for a striking absence of overwhelmed hospitals, and for low reported mortality. The marked contrast with the overwhelmed hospitals and high mortality seen in Europe and other high income settings was regarded as "puzzling" or a "paradox". We reflect on possible explanations for this paradox with particular reference to observations made "on the ground" in Kenya.

We identify sufficient evidence to reject many potential explanations for the differing epidemiology in Africa. Longitudinal surveillance using antibody assays suggested that viral transmission was widespread and rapid. These data contradict explanations such as: an impact of climate on virus droplets; enhanced air circulation in rural settings; or stringent and effective public health interventions against infectious spread. We acknowledge resource limitations on surveillance of severe disease in hospitals and registration of deaths, but nevertheless identify sufficient evidence to exclude hidden hospital surges, and to exclude a hidden substantial death rate outside hospital.

Population age structure is an important but incomplete explanation of the epidemiology. The simplistic calculation of multiplying infection-fatality rates by the Kenyan population age structure implies a figure substantially higher than the observed excess deaths, and the calculation is further misleading because the infection fatality rates were derived from settings where the health system capacity mitigated the risk of death. Multiplying infection-hospitalization rates by the age structure of the Kenyan population predicts over a million hospital admissions, which would have been well beyond the surge capacity of the Kenyan healthcare system, and incompatible with the data showing that substantial hospital surges were not seen.

We found a very high prevalence of asymptomatic infection in routine data as well as in longitudinal studies with active surveillance. Taking this together with the lack of hospital surges, the low mortality estimates, and the evidence against reduced viral transmission, we conclude the primary explanation for the "paradox" is reduced susceptibility to symptomatic disease among populations in Africa.

There is an opportunity to further study pre-pandemic immunity and other potential mechanisms for the reduced susceptibility to severe COVID in Africa. Given our incomplete understanding of the mechanisms associated with reduced susceptibility to severe COVID, we should not be complacent about health security in Africa, and should prioritize the rapid acquisition of data on the ground to guide future pandemic responses.

Main Text

The first cases of COVID were reported in Africa in Egypt and in Nigeria in February 2020, and in Kenya in March 2020. COVID cases were subsequently identified in all parts of Africa. International agencies were guided by analyses predicting millions of COVID related deaths in Africa(*1*), and advised that there were limited options for mitigation of the impending disaster on the continent(*2*). Many countries in Africa responded by taking immediate firm action including lockdowns and social restrictions, considering the attendant economic and public health costs justified by the impending disaster(*3*). As the pandemic progressed, the experience in Africa was striking for the absence of overwhelmed hospitals struggling to cope with surges of patients with severe COVID, and for relatively few deaths. Notable exceptions, where hospital surges were frequently seen, included North African countries and South Africa(*4*, *5*). There were media reports of mass graves in New York(*6*) and Manaus(*7*), but not in most of Africa, despite modelled predictions of high numbers of deaths(*8*). The contrast between these experiences in Africa and the very obvious hospital surges in Europe, the Americas, and Asia was regarded as "puzzling"(*9*) or as a "paradox"(*10*). Explanations put forward included the early and stringent public health interventions, altered transmission due to climate or ventilation, pre-pandemic population immunity, the younger population, or poor surveillance systems leading to erroneous data. Here, we reflect on these possibilities with particular reference to observations made "on the ground" in Kenya, where we worked throughout the pandemic. We consider published data on initial transmission (i.e. serological surveys), hospital admission data, demographic surveillance for mortality, routine testing data, contextualizing these observations with work undertaken elsewhere.

How rapid and how widespread was SARS-CoV-2 transmission in Africa?

One group of potential explanations is that the transmission of SARS-CoV-2 was lower in Africa, either because of environmental or human factors. Specific explanations might include: climate and seasonal effects on viral persistence in the environment(*11*); early and/or stringent public health interventions; improved air circulation in rural environments; or social policy (*12*). These explanations would be evidenced by a substantial reduction in the rates of person-to-person transmission of SARS-CoV-2 in Africa.

In Kenya, figures from PCR testing in routine surveillance might have been taken to support reduced person-to-person transmission: at three months after the first case only 20,000 cases had been identified (i.e. affecting <0.1% of the population). However, a contemporaneous nationwide serological survey of blood donors using a well validated assay(*13*, *14*) indicated that exposure was more widespread, with anti-SARS-CoV-2 antibodies present in 4.3% of the population(*15*). In contrast, 9 months after the first cases were seen in the UK, anti-SARS-CoV-2 antibody prevalence ranged from 3% to 10% depending on geography(*16*). Both the Kenyan and the UK figure would have been impacted by lockdowns and many other factors: nevertheless the comparison implies that the rates of viral spread in Kenya and the UK were comparable. Further serological studies in Kenya indicated that antibody

prevalence reached 22% in Nairobi, the capital city, by six months (*17*); community-based surveys undertaken a year later indicated antibody prevalences in diverse geographical settings at 24-50% of the Kenyan population (*18*); and surveys in 2022 found that 72-94% of the population were positive, indicating nearly universal exposure in some geographical locations (*19*). Our data on rapid spread in Kenya is consistent with antibody surveys undertaken in Malawi(*20*), Ethiopia(*21*) and Nigeria(*22*).

In Kenya, we further developed transmission models incorporating these serological surveys and PCR testing. We found that initial transmission was focused on less privileged socioeconomic groups in urban centres, subsequently spread to more privileged socioeconomic groups, and then spread further to rural areas later in the epidemic(*23*). There were similar findings in South Africa(*24*), likely indicating that the ability to adhere to social restrictions depends on socioeconomic privilege, and resulting in an early "double peak" of cases in Kenya(*23*). Subsequent peaks in transmission occurred due to the introduction of new variants, which similarly spread widely through the population(*25*, *26*).

Taken together, the rapid spread through urban and rural environments in Kenya provide little support for climate, outdoor living, lack of population mixing, social interventions or other factors acting on viral transmission as explanations for the contrasting epidemiology seen.

A variation on this group of explanations is that lower infectious inoculums (e.g. from outdoor, well ventilated settings) might still lead to infections, albeit with reduced severity. The link between inoculum and severity is supported by animal models(*27*). However, if conditions led to systematically lowered inoculums this would necessarily imply reduced infectiousness, which seems inconsistent with the evidence of rapid spread of the virus through both rural and urban populations discussed above(*17*, *19*), and furthermore at least 40% of the population in sub-Saharan Africa live in urban conditions.

Were there hospital surges due to COVID in Africa?

There were overwhelming surges of COVID admissions around the world, including in the USA(*28*), Europe(*29*) and in South Africa(*30*). There were recorded case series of severe COVID from countries in the rest of Africa, including Kenya(*31*) and in Malawi(*32*), and isolated health care worker deaths were reported(*33*), but without increasing detectable increase in total hospital admissions(*34*). Prospective data from 13 hospitals in Kenya indicated that public hospitals had consistent patient numbers throughout the pandemic waves(*35*). We noted a modest increase in the diagnosis of severe acute respiratory illness coinciding with periods of increased COVID transmission in the community, but there was no corresponding increase in overall patient numbers or any increase in mortality among those admitted. Furthermore, there was no evidence that hospital surges were masked by compensatory displacement of other activity: despite initial disruption of routine community services such as vaccination and malaria prevention due to social distancing policies, there was a rapid return to normal levels of activity including "catch up" campaigns(*36*–*38*). Given the public interest it seems unlikely that the reality of collapsing healthcare could have been completely hidden from the media (*39*), and taken together with the data reviewed above, we consider it unlikely that there were hidden hospital surges across Africa.

Was there a high death rate in the community without accessing hospital care?

Access to care is limited in many parts of Africa, hence complete estimates of mortality require data from the community as well as hospital surveillance(*40*). The balance of community versus hospital

disease burden might be further shifted to the community by the fear associated with COVID leading to hospital avoidance(*41*), and might explain the "COVID paradox" in Africa if the low hospital numbers are associated with substantial undetected disease in the community. The likely outcome of absent hospital care for severe COVID would be high death rates. While mass graves were reported in New York(*6*) and Manaus(*7*), there were no similar reports from Africa. Nevertheless, given the limited vital registration data, underreporting of mortality in the community was considered a possible explanation(*42*).

Models to predict mortality in the absence of vital registration were constructed using parameters estimated from outside Africa, and/or from North Africa and South Africa. One model indicated more than a million deaths in sub-Saharan Africa(*43*), another indicated just over a million in East Africa alone(*44*). Furthermore, some direct observations were supportive of high death rates in Africa. A study in Zambia was undertaken using post-mortem PCR testing in Lusaka Hospital, and a high prevalence of SARS-CoV-2 virus was found(*45*). However, there were no contemporaneous data on the community prevalence of SARS-CoV-2 in Lusaka that could be used to calculate attributable mortality. For instance, 20% of all deaths in the 10-19 year old age range in Lusaka Hospital were associated with PCR positivity. Given the rarity of death due to COVID in this age range, it would seem more likely that most of the positive results in this age range indicated coincidental infection rather than the proximate cause of death. We cannot know the extent to which this was true of older age groups.

Direct estimates of excess deaths were generally considered to not be possible using the limited civil registration systems available(*46*). In place of complete civil registration, research centres undertake demographic surveillance systems (DSS) as sentinel surveillance of births and deaths(*47*, *48*). DSS studies in The Gambia(*49*) and coastal Kenya (i.e. Kilifi) have been used to estimate excess deaths during the pandemic(*50*).

In Kenya, among >300,000 residents of the Kilifi DSS, observed and expected deaths among those aged ≥1 year were 2441 and 2276, respectively, giving an excess mortality rate of 31.0/100,000 person-years and implying 13,700 excess deaths in Kenya as a whole. This excess death figure is roughly twice the 5,400 deaths identified from routine surveillance in official statistics(*51*). Generalizing data from Kilifi to the rest of Kenya is vulnerable to geographical heterogeneity. Kilifi County appears to have had average social and below average epidemiological vulnerability to COVID compared with the rest of Kenya(*52*). Furthermore, while routine statistics would be expected to underestimate mortality directly due to COVID, the DSS estimate of excess deaths includes the sum of deaths caused directly or indirectly by COVID, or caused by other temporal fluctuations. Nevertheless, the figure of 13,700 excess deaths is lower than those implied for Kenya by international models: 17,000 deaths by WHO AFRO(*53*); 28,000 by WHO(*43*); 117,000 by the Economist (*8*); and 171,000 by IHME(*44*).

Parallel figures from The Gambia showed a consistent pattern. In DSS studies covering a population of >250,000 residents in Basse, Farafenni and Keneba in The Gambia, observed deaths ranged from 1438 to 1606 per year pre-COVID; and were 1634 during 2020. This indicated an excess death rate of 11.1 per 100,000 or 308 excess deaths nationally (*49*), compared with: 343 COVID deaths in official statistics from surveillance data(*51*); 1,450 deaths in the WHO AFRO model(*53*); 1,578 by WHO(*43*); 3,442 by The Economist(*8*); and 6,340 by IHME(*44*).

Taken together, the direct observations based on DSS studies are more consistent with the lower modelled estimates. We have limited data to examine causes of death or care pathways, but we can conclude that there was detectable excess mortality at a population level in Kenya. However, had

deaths outside hospital been the explanation for the absence of hospital surges in Africa, then this would have implied several hundred thousand COVID deaths in the absence of hospital care, and the observed excess mortality is incompatible with this number.

Could the lower average age in Africa explain the mortality difference?

The average ages of the USA, South Africa and Kenya are 38.9, 26.9 and 19.6, respectively. The infection fatality rate due to COVID varies markedly by age. International data indicated that the infection fatality rate rose from: 0.01% at age 25-29; through 0.1% at age 40-45; to 1% at age 65-70(*54*). The theoretical mortality from a single COVID exposure to the Kenyan population can be calculated from multiplication of infection fatality rates by the Kenyan population age structure: giving a figure of approximately fifty thousand deaths. This may indicate reduced susceptibility a priori, as fifty thousand is, for instance, many fewer than the two hundred thousand deaths recorded in the UK despite access to vaccination and other mitigations in the UK(*51*). On the other hand, fifty thousand is substantially higher than the 5,400 deaths implied by generalizing the DSS surveillance.

A calculation based on a single exposure of the population might be mitigated by data showing that the first infection with SARS-CoV-2 accounted for the majority of severe disease(*55*, *56*), and by data showing widespread serological evidence of exposure in Kenya(*23*). However, the infection fatality rates include the impacts of the health system, which was heavily utilized in countries where the infection fatality rates were first derived. Specific healthcare interventions reduce the mortality due to COVID(*57*, *58*) and the more general impact of healthcare is evident through increased mortality when the hospital surge capacity is exceeded(*28*, *29*).

The parallel calculation of multiplying infection-hospitalization rates by the age structure of the Kenyan population predicts a total of over a million hospital admissions with severe COVID(*59*). Capacity in the Kenyan healthcare system is orders of magnitude below these levels(*60*), and as described above, there was no indication of substantial hospital surges in Kenya(*35*). It might be assumed that African countries have less prevalent comorbidity than high income settings, but on the other hand some relevant comorbidities are more prevalent in Africa, such as tuberculosis, malnutrition and HIV (*61*). In Kenya we noted a substantial prevalence of risk factors including HIV (5%), diabetes (2.4%), hypertension (24%) and obesity (27%)(*52*). Models that adjusted for comorbidity prevalence in Kenya still predicted nearly a million admissions to hospital with COVID in Kenya(*62*).

Hence, at the onset of the pandemic it might have been argued that the age structure would predictably lead to reduced mortality compared with European countries, on the other hand it would have been unsafe to entirely base policy on this without very substantial investment to increase surge capacity in the health system. Furthermore, the absence of the hospital surges and the even lower mortality observed in Kenya suggest that age structure can only be a partial explanation of the "COVID paradox".

What symptoms did SARS-CoV-2 cause in the community in Kenya?

Although high numbers of symptomatic cases were reported in South Africa and in North African countries, this was less evident in other parts of Africa. In Kenya, we found that the prevalence of asymptomatic infection among participants undertaking routine testing was as high as 97%(*63*). Tests from 97,124 asymptomatic participants were positive 7% of the time compared with only 24% of 2,568 tests from participants with symptoms, suggesting a very high prevalence of asymptomatic infection.

Passively acquired routine data may be biased by treatment seeking behavior (for instance if most symptomatic patients avoid testing, but asymptomatic individuals are tested to facilitate travel or work), but findings from active surveillance of cohorts in Kenya were similar.

In a vaccine trial that included active surveillance for infection through 7 scheduled clinic visits for 400 participants, we identified 87 cases of SARS-CoV-2 infection, all of which were asymptomatic(*64*). Furthermore, in a longitudinal study of households with index cases, 43 secondary cases were identified and followed up for two weeks, during which 21% reported symptoms in their daily symptom diaries(*65*). All but one of these symptoms were limited to a single day's duration, and the prevalence of symptoms was similar among PCR positive compared with PCR negative individuals (i.e. 21% vs 18%).

We conclude that the majority of infections in Kenya with SARS-CoV-2 were asymptomatic. The prevalence of asymptomatic infection was much lower outside Africa: where roughly half of all infections appeared to be asymptomatic(*66*, *67*). In contrast to the impact of age on the risk of severe disease, age has only a modest impact on the risk of non-severe symptomatic disease. For instance, in meta-analyses 47% of younger adults and 32% of children have asymptomatic infection compared with 20% of older adults(*66*), hence the younger average age in Kenya does not explain the >80% prevalence of asymptomatic infection in both routine testing data and longitudinal cohorts.

Data from Kenya are consistent with data from Nigeria where 75% of infections in routine testing data were asymptomatic(*68*) and contract tracing studies where symptoms were also poorly predictive of SARS-CoV-2 infection(*69*). Frequent asymptomatic infections were also noted in community surveys in Malawi(*70*).

Are there plausible biological explanations for a less marked host response?

The high prevalence of asymptomatic infection, the lack of severe disease leading to hospital surges, and the reduced mortality overall suggests a reduced host propensity to developing mild or severe disease at the centre of the "COVID paradox". Genetic factors are well established as risk factors for severe COVID(*71*) and HLA markers may be associated with asymptomatic infection due to cross-reactive T cell responses(*72*). However, there was an increased risk of hospitalization and death seen among populations of African descent in the US and in Europe(*73*–*75*). In theory, populations of African descent in high income settings could experience balancing impacts of socioeconomic status versus genetic protection in the US and UK, but nevertheless this implies that any genetic protection is unlikely to be a primary explanation for the epidemiology of COVID seen in Kenya and elsewhere in Africa.

Vitamin D status has been associated with less severe COVID and might be considered a potential reason for lessened mortality in Africa. However, the protective efficacy of vitamin D status is modest(*76*), the direction of causality has been contested(*77*) and vitamin D status is in fact not uniformly high across Africa(*78*).

The diagnostic antibody surveillance detailed above found a very low prevalence of antibodies prior to the pandemic(*15*, *79*). More detailed studies showed some evidence of cross-reactive neutralizing antibodies prior to the pandemic in Kenya(*80*), but these cross-reactive antibodies were also found in Europeans(*81*), and were rare in both Kenya and Europe.

Further data are needed on T cell responses to SARS-CoV-2 in Africa, particularly given the evidence linking pre-pandemic T cell responses with protection (*82*) and a higher prevalence of asymptomatic

infection(*72*). Pre-pandemic T cell responses might be acquired by prior exposure to an infectious agent circulating predominantly in Africa with cross-reactive T cell epitopes. Alternatively, prior exposures may impact susceptibility through bystander effects that reduce pro-inflammatory responses and/or promote regulatory responses(*83*, *84*).

The distribution of high COVID mortality in North Africa and South Africa and low mortality on the rest of the continent also requires explanation, and the geographical distribution of risk led some to suggest that falciparum malaria generated prior immunity against COVID(*85*). However, central Kenya experiences very low malaria transmission, and yet hospitals in central Kenya showed no evidence of higher COVID caseloads than hospitals in the west of Kenya which experiences high malaria transmission(*35*). Besides malaria, there are likely many known and unknown infectious exposures that have distinct biogeography(*86*), and that may share epitopes with SARS-CoV-2 or have bystander impacts on inflammatory responses(*87*, *88*). Other potential factors for more severe outcomes in North African countries and in South Africa include older and more comorbid populations(*89*, *90*) and as yet unknown genetic factors that may segregate geographically within Africa(*91*).

Conclusion

The data indicate a reduced susceptibility to severe illness and mortality associated with SARS-CoV-2 infection in Kenya. A lower average age may be an important, but incomplete explanation. The prevalence of asymptomatic infection, taken together with data linking asymptomatic infection to HLA types and cross-reactive T cell responses, may invite speculation about pre-pandemic immunity due to other infectious agents. Whatever the explanation was for resilience to COVID, it does not appear to have generalized to the 1918 Influenza pandemic. There are records of devastating mortality in 1918 across Africa(*92*) including Nigeria(*93*) and Kenya(*94*) and the records of high mortality in 1918 in Kilifi sharply contrast our data from the same county during COVID(*95*). A further contrast between the 1918 and 2020 pandemics was the inverse relationship with age (i.e. higher mortality in young adults in 1918(*96*), versus lower mortality in young adults in 2020). Hence, it seems prudent that policy makers faced with limited data to guide them as COVID spread to Africa took early firm action.

Health security in Africa remains fragile for future pandemics(*97*), for which rapid acquisition of data on the ground should be prioritized over externally-led models and analysis generalizing from external sources(*98*). Effective vital registration systems, demographic surveillance at sufficient scale to monitor mortality, and sentinel hospital surveillance provide essential data to guide pandemic responses. A focus on local data will facilitate better informed models, cost-effective policy(*99*) and public health policy that evolves with the reality on the ground rather than external perceptions. .

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