Rethinking the Evidence on COVID in Africa

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Key Points

1. The experience of COVID in Africa did not indicate the expected morbidity and mortality across the entire continent. We review the evidence available in order to determine whether reduced viral transmission, public health interventions, poor surveillance, or biological explanations are plausible.
2. High mortality and morbidity was well documented in some African Countries such as South Africa, and in Northern African Countries. Data are patchy across the rest of Africa, but indicate low mortality in community surveys in Kenya and in the Gambia, a lack of hospital surges, and intermediate mortality in some countries such as Madagascar.
3. There was evidence of widespread viral transmission when studied, consistent with observations outside Africa.
4. Population age structure is an important but incomplete explanation of the reduced mortality.
5. Taking together the high prevalence of asymptomatic infection and low mortality, and evidence of reduced inflammatory responses, we conclude that certain populations in Africa have reduced susceptibility to symptomatic COVID.
6. When responding to global pandemics, local data are essential to develop public health policies that accord with the reality on the ground rather than external perceptions.

Summary

The COVID pandemic was predicted to cause substantial mortality in Africa. However, experiences from some 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. The evidence is inconsistent with reduced viral transmission or poor surveillance as primary explanations. Population age structure is an important but incomplete explanation of the epidemiology. Taking together the high prevalence of asymptomatic infection and low mortality with evidence of reduced inflammatory responses, we conclude that certain populations in Africa have reduced susceptibility to symptomatic COVID. The reduced inflammatory responses may result from immunoregulation and/or cross-reactive pre-pandemic cellular immunity. Local data are essential to develop public health policies that accord with the reality on the ground rather than external perceptions.

Review 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 from some countries 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.

There were media reports of mass graves in New York[4] and Manaus[5], but not in countries such as Kenya or Nigeria, despite modelled predictions of high numbers of deaths[6]. Notable exceptions, where hospital surges were frequently seen, included North African countries and South Africa[7,8]. The contrast between some African countries 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 parts of 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 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.

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

The most common form of COVID reported worldwide was a self-limiting febrile illness with respiratory symptoms. High numbers of symptomatic cases were reported in South Africa and in North African countries through routine surveillance. In Kenya, we found that the prevalence of asymptomatic infection among participants undertaking routine testing was as high as 97%[28]. 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. However, routine data may be biased by treatment seeking behavior (for instance if most symptomatic patients avoid testing, but asymptomatic individuals are tested in high numbers).

Active surveillance for SARS-CoV-2 was undertaken in a vaccine trial that included 7 scheduled clinic visits for 400 participants. This trial identified 87 cases of SARS-CoV-2 infection, all of which were asymptomatic[29]. 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[30]. 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%).

Taking the routine data and these active cohorts together, we conclude that the majority of infections in Kenya with SARS-CoV-2 were asymptomatic.

Data from Kenya are consistent with data from Nigeria where 75% of infections in routine testing data were asymptomatic[31] and where symptoms were found to be poorly predictive of SARS-CoV-2 infection in contract tracing studies[32]. Frequent asymptomatic infections were also noted in community surveys in Malawi[33], and in a community survey in Guinea Bissau [34].

The prevalence of asymptomatic infection was much lower outside Africa: where roughly half of all infections appeared to be asymptomatic[35,36]. 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[35], hence the younger average age in Kenya would not explain the >80% prevalence of asymptomatic infection in both routine testing data and longitudinal cohorts.

On the other hand, the prevalence of asymptomatic infection was 45% in South Africa [37], 38% in Egypt[38], and 30% in Madagascar[39], indicating that the high prevalence of asymptomatic infection seen in Nigeria, Malawi and Kenya did not generalize to all countries in Africa.

Long COVID causes substantial morbidity in high income settings. It appears that asymptomatic infection may give rise to long COVID. However, definitions of long COVID are contested and most reports have depended on identifying symptomatic episodes[40]. There has been limited study in Africa. Two recent systematic reviews identified very few studies outside North Africa and South Africa, leaving substantial uncertainty about the long term social and economic consequences of infection for many African populations[41,42].

Were there hospital surges due to COVID in Africa?

There were overwhelming surges of COVID admissions around the world, including in the USA[40], Europe[41] and in South Africa[42]. There were recorded case series of severe COVID from countries in the rest of Africa, including Kenya[43] and in Malawi[44], and isolated health care worker deaths were reported[45], but without increasing detectable increase in total hospital admissions[46]. A study including hospitals in Democratic Republic of the Congo, Ghana, Kenya, Nigeria, South Africa, and Uganda indicated that most children or adolescents with severe COVID had substantial comorbidities, among whom mortality was 8% [50]. Prospective data from 13 hospitals in Kenya indicated that public hospitals had consistent patient numbers throughout the pandemic waves[47]. Six of these hospitals were designated COVID-19 treatment centres, and all 13 were typical “district-level” health facilities, including the Coast, Central and Western Kenya. 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[48–50]. Given the public interest it seems unlikely that the reality of collapsing healthcare could

have been completely hidden from the media [51], 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[52]. 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[53], 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[4] and Manaus[5], 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[54].

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[55], another indicated just over a million in East Africa alone[56]. 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[57]. 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[58]. In place of complete civil registration, research centres undertake demographic surveillance systems (DSS) as sentinel surveillance of births and deaths[59,60]. DSS studies in The Gambia[61] and coastal Kenya (i.e. Kilifi) have been used to estimate excess deaths during the pandemic[62].

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[63]. 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[64]. The figure of 13,700 excess deaths is lower than those implied for Kenya by international models: 17,000 deaths by WHO AFRO[65]; 28,000 by WHO[55]; 117,000 by the Economist [6]; and 171,000 by IHME[56].

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 [61], compared with: 343 COVID deaths in official statistics from surveillance data[63]; 1,450 deaths in the WHO AFRO model[65]; 1,578 by WHO[55]; 3,442 by The Economist[6]; and 6,340 by IHME[56].

In Madagascar, based on death surveillance in the five districts of Antananarivo, 1179 excess deaths were reported. Normalized to the general population of Madagascar, the number of excess deaths were 38.51 and 64.91 per 100 000 inhabitants in 2020 and 2021, respectively [66]. This implies 30,000 excess deaths nationally, compared with the 1,426 identified on routine statistics, and compares with: 9,822 deaths by WHO AFRO [65]; 46,642 by WHO [55]; 46,737 by the Economist [6]; and 65,100 by IHME [56].

In South Africa, national vital registration data measured excess deaths at just under 300,000 [67], compared with 91,564 deaths were reported through direct surveillance. These compare with: 92,118 by WHO AFRO [65]; 247,000 by WHO [55]; 273,110 by the Economist [6]; 302,000 by IHME [56].

Hence, in all four countries the excess mortality calculated from community surveillance implied more deaths than those identified by health service surveillance of COVID related deaths. In limited resource settings, routine healthcare surveillance underestimates COVID mortality due to missing data. Furthermore, excess mortality includes the sum of deaths caused directly or indirectly by COVID, deaths related to associated healthcare or economic impacts, and deaths from other unrelated causes. Combinations of these latter factors have been proposed to explain the patterns of excess mortality in high income settings. However, in Kenya, South Africa and Madagascar where significant excess mortality was identified, the timing of deaths aligned with waves of COVID, implicating underestimated of mortality in healthcare surveillance as the primary explanation for the gap.

Furthermore, in Gambia and Kenya the excess mortality calculated from community surveys was substantially lower than the predictions from international models, in Madagascar the excess mortality from community surveys was in the lower range of predictions from models, and in South Africa the community surveys and model predictions were aligned (Table 1).

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[68]. 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[63]. 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[69,70], 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[71,72] and the more general impact of healthcare is evident through increased mortality when the hospital surge capacity is exceeded[40,41].

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[73]. Capacity in the

Kenyan healthcare system is orders of magnitude below these levels[74], and as described above, there was no indication of substantial hospital surges in Kenya[47]. 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 [75]. In Kenya we noted a substantial prevalence of risk factors including HIV (5%), diabetes (2.4%), hypertension (24%) and obesity (27%)[64]. Models that adjusted for comorbidity prevalence in Kenya still predicted nearly a million admissions to hospital with COVID in Kenya[76].

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 is only a partial explanation of the "COVID paradox".

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" in Kenya. In contrast, asymptomatic SARS-CoV-2 infection was less prevalent in Madagascar and in South Africa, where higher mortality appears to have been observed.

Genetic factors are well established as risk factors for severe COVID[77] and HLA markers were associated with asymptomatic infection[78]. However, in addition to the variation in outcomes across Africa, there was an increased risk of hospitalization and death seen among populations of African descent in the US and in Europe[79–81]. Taken together, this implies that genetic factors are 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[82], the direction of causality has been contested[83] and vitamin D status is in fact not uniformly high in populations across Africa[84].

The diagnostic antibody surveillance detailed above found a very low prevalence of antibodies prior to the pandemic[15,85]. More detailed studies showed some evidence of cross-reactive neutralizing antibodies prior to the pandemic in Kenya[86], but these cross-reactive antibodies were also found in Europeans[87], and were rare in both Kenya and Europe.

Further data are needed on pre-pandemic T cell responses to SARS-CoV-2 in Africa, particularly given the evidence linking pre-pandemic T cell responses with protection [88] and a higher prevalence of asymptomatic infection[78]. 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[89,90]. Furthermore, reduced inflammatory responses were seen among Senegalese patients with COVID compared with Europeans, including an absence of inflammasome and neutrophil activation[95]. Other studies report cytokine profiles consistent with these findings in Malawi[96,] in Ghana[97], and in Kenya[91].

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[92]. 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[93], and malaria endemicity is higher in Madagascar where COVID outcomes appear to have been worse than in Kenya.

Besides malaria, there are likely many known and unknown infectious exposures that have distinct biogeography[94], and that may share epitopes with SARS-CoV-2 or have bystander impacts on inflammatory responses[95,96]. Other potential factors for more severe outcomes in North African countries and in South Africa include older and more comorbid populations[97,98].

Taking these findings together, we propose that the primary explanation for the epidemiology seen in countries with less severe COVID outcomes is pre-pandemic multiple infectious exposures, leading to cross-reactive T cell responses (but not cross reactive antibodies), the outcome of which is less inflammatory cytokine responses on exposure to SARS-CoV-2. These lower inflammatory responses result in a high frequency of asymptomatic infection, but nevertheless allows transmission to proceed. In South Africa and Madagascar, higher mortality and morbidity was reported, and asymptomatic infection was less frequent. We therefore speculate that this might be explained by different pre-pandemic infectious exposures and more inflammatory cytokine responses. Furthermore, while we identify data from some countries indicating epidemiological outcomes that diverged from expectations, the data are patchy and insufficient to generalize across Africa.

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 leading to an attenuated inflammatory response on infection with SARS-CoV-2. 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[99] including Nigeria[100] and Kenya[101] and the records of high mortality in 1918 in Kilifi sharply contrast our data from the same county during COVID[102]. A further contrast between the 1918 and 2020 pandemics was the inverse relationship with age (i.e. higher mortality in young adults in 1918[103], 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. Restrictions initially interrupted other public health activities[111,112] including malaria control[113]. However, there was evidence that public health activities rapidly made up the lost ground as restrictions were lifted[114,115], demonstrating the value of responding to local data.

Health security in Africa remains fragile for future pandemics[3], for which rapid acquisition of data on the ground should be prioritized over externally-led models and analysis generalizing from external sources[104]. Data in resource limited circumstances are patchy , requiring prioritization of the most informative and cost effective surveillance modalities[117]. 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[105,106] and public health policy that evolves with the reality on the ground rather than external perceptions.

Search strategy and selection criteria

We searched PubMed and Google Scholar using terms specific for the topics of interest within each section of the review in turn (i.e. "Transmission", "Serology", "Testing", "Asymptomatic" "Excess Mortality" "DSS" "Surveillance"), combined with the following Boolean search terms: AND ("COVID" OR "SARS-CoV-2") AND ("Africa"). For key commentaries (i.e. Happi et al, 2022 and Maeda et al, 2021, and "Pandemic's True Death Toll", The Economist 2021), we examined referenced articles, and citing articles using Google Scholar. We included press articles to illustrate selected points without systematic searches. The review was limited to English language articles. No date restriction was used. Inclusion criteria were not systematic and articles were included based on relevance to the narrative review.

Acknowledgements

Work was supported by a core Wellcome award (203077/Z/16/Z) and drafting the manuscript was clarified by participation in a workshop "COVID-19 and Africa: Equations, Epistemologies, and Experiences" funded by AfOx and organized by Tolulope Osayomi (University of Ibadan, University of Oxford AfOx Visiting Fellow) and Erica Charters (University of Oxford, Faculty of History). Bob Snow is thanked for comments on a draft manuscript. Publication is by permission of the KEMRI Director General.

The authors declared no conflicts of interest. Contributions were: first draft (PB); concept (PB, EB); revisions and development (PB, AA, IO, MH, DK, SM, EB)

Table 1: Deaths identified by direct observation compared with modelled estimates

Country	DSS Survey	Predicted National Excess Mortality	Routine Surveillance Deaths	WHO AFRO	WHO	Economist	IHME
Kilifi, Kenya[120]	31.0/100,000	13,700	5,400	17,000	28,000	117,000	171,000
The Gambia[65]	11.1/100,000	308	343	1,450	1,578	3,442	6,340
Madagascar[70]	38 and 65 per 100,000	30,000	1,426	9,822	46,642	46,737	65,100
South Africa[71]	NA	300,000	91,564	92,118	247,000	273,110	302,000

Footnote: South African data to predict national excess mortality depend on vital registration rather than Demographic Surveillance (DSS). The modelled mortality estimates come from the WHO AFRO[69], WHO[59], Economist[6] and IHME[60] models as published.

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