Leveraging Serosurveillance and Postmortem Surveillance to Quantify the Impact of COVID-19 in Africa

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Running Title: COVID-19 Underascertainment in Africa

Abstract

Background

The COVID-19 pandemic has had a devastating impact on global health, the magnitude of which appears to differ intercontinentally: for example, reports suggest 271,900 per million people have been infected in Europe versus 8,800 per million people in Africa. While Africa is the second largest continent by population, its reported COVID-19 cases comprise <3% of global cases. Although social, environmental, and environmental explanations have been proposed to clarify this discrepancy, systematic infection underascertainment may be equally responsible.

Methods

We seek to quantify magnitudes of underascertainment in COVID-19's cumulative incidence in Africa. Using serosurveillance and postmortem surveillance, we constructed multiplicative factors estimating ratios of true infections to reported cases in Africa since March 2020.

Results

Multiplicative factors derived from serology data (subset of 12 nations) suggested a range of COVID-19 reporting rates, from 1 in 2 infections reported in Cape Verde (July 2020) to 1 in 3,795 infections reported in Malawi (June 2020). A similar set of multiplicative factors for all nations derived from postmortem data points toward the same conclusion: reported COVID-19 cases are unrepresentative of true infections, suggesting a key reason for low case burden in many African nations is significant underdetection and underreporting.

Conclusions

While estimating COVID-19's exact burden is challenging, the multiplicative factors we present furnish incidence estimates reflecting likely-to-worst-case ranges of infection. Our results stress the need for expansive surveillance to allocate resources in areas experiencing discrepancies between reported cases, projected infections, and deaths.

Keywords: COVID-19, serology, postmortem surveillance, underreporting, cumulative incidence

Introduction

To date, coronavirus disease 19 (COVID-19) has led to a reported 605 million cases and 6.5 million deaths globally [1]. Asia, North America, South America, and Europe have respectively contributed 180 million, 112 million, 63 million, and 224 million cases to this toll (roughly 39,465; 193,400; 149,100; and 300,100 cases per million population) and over 1.3 million deaths each, whereas reported COVID-19 morbidity and mortality appear lower in Africa: 12 million cases (8,800 cases per million population) and 255,000 deaths [1, 2].

This observation has led some to conclude the pandemic has "spared" Africa and parts of Asia [3]. Several explanations have been proposed, including swift government response, young age structure, sparse population density, competing comorbidities, and climate effects. However, the World Health Organization (WHO) has posited that systematic underascertainment explains continental differences in reporting, further estimating that only 1 in 7 COVID-19 cases in Africa have been detected compared to 1 in 4 COVID-19 cases in the United States [3-8]. This hypothesis has been bolstered by several recent national and sub-national studies [3, 9].

Variability in underascertainment reported by these studies motivates practicable methods that can triangulate between disparate data sources to provide credible estimates of African nation-specific COVID-19 infections. While the exact number of infections can never be known, producing a range of estimates reflective of likely- and worst-case scenarios remains valuable in understanding the burden of disease. Here we propose 2 methods that approximate the magnitude of COVID-19 cumulative incidence in Africa, the first relying on serosurveillance data and the second relying on postmortem surveillance data.

Methods

Motivation for Serosurveillance

National population-based serosurveys furnish cross-sectional estimates of cumulative incidence of infection by SARS-CoV-2 in quantifying proportions of a population with SARS-CoV-2 antibodies ("seroprevalence"). Relevant for infection are antibody isotypes IgA, IgG, and IgM, further classifiable based on specificity for SARS-CoV-2 spike (S), receptor binding domain (RBD), or nucleocapsid (N) proteins [10, 11]. Antibody specificity can also help differentiate between antibody production due to natural infection versus vaccination (coverage for which is still low in Africa), with the latter observed to induce production of anti-S and anti-RBD – but not anti-N – antibodies [11-13].

Inferring Infection Underascertainment: Analysis of Serosurveillance Data

Using SeroTracker, a global SARS-CoV-2 seroprevalence database, we identified 29 national-level serosurveys collected throughout the pandemic across 12 African nations: Cape Verde, Côte d'Ivoire, Egypt, Ethiopia, Gabon, Ghana, Kenya, Malawi, Senegal, Sierra Leone, South Africa, and Zambia [14]. Table 1 includes seroprevalence point estimates and 95% confidence intervals (where available) as well as a sample of serosurvey metadata furnished by SeroTracker. [15].

For each of the 12 African nations, seroprevalences were compared to the proportion of that nation's population reported to have COVID-19. The latter proportion was obtained by dividing reported cumulative cases (Our World in Data) at the end of the serosurvey sampling period by the nation's 2020 or 2021 population [16, 17]. Hereafter, we refer to the ratio of seroprevalence to this proportion as a "multiplicative factor", extending the work of Angulo et al.

(2021) who previously formulated a similar procedure to estimate COVID-19 infections, hospitalizations, and deaths in the United States [9].

A multiplicative factor of 1 suggests complete concordance in population positivity for COVID-19 between serology reports and case reports – equivalently, no apparent underascertainment. In contrast, a multiplicative factor greater than 1 suggests serology-derived estimates of infection incidence exceed reported cases, reflective of "hidden morbidity". Multiplicative factors are expected to be greater than 1 due to the large number of asymptomatic COVID-19 infections that go undetected, insensitivity of tests, failure to report positive tests, and/or absence of testing among population strata. Applying multiplicative factors to nation-specific epidemic curves produces scaled curves reflecting infection incidence while maintaining local-in-time trends (Figure 1). To limit overextrapolation, these scaled curves were only projected to the nearest half-year. Although there is a 1- to 2-week delay between infection and seropositivity, lagged reporting of infections counteracts the effect of this delay [18, 19].

Inferring Infection Underascertainment: Analysis of Postmortem Surveillance Data

To create another set of multiplicative factors, we drew from 2 Zambian postmortem surveillance studies using quantitative reverse transcription PCR to detect COVID-19 in decedents: Mwananyanda et al. (2021), conducted in June – October 2020 following the first infection wave, and its preprinted (not yet peer-reviewed) follow-up from Gill et al. (2022), conducted in January – June 2021 following the second infection wave [20-22].

Prior to these studies, fewer than 10% of deaths attributed to or related to COVID-19 in Lusaka were identified in life with antemortem testing [19]. In contrast, the 2 postmortem studies found that 58 of 364 (15.9%) decedents in the first and 358 of 1,116 (32%) decedents in the

second were PCR-positive, suggesting underascertainment of COVID-19 cases and deaths. Of the 364 decedents recruited by Mwananyanda et al. (2021), 96 (26%) occurred in a clinical facility and 268 (74%) occurred in a community setting (outside of medical care), compared to 573 (51%) facility and 543 (49%) community deaths in Gill et al. (2022).

Noting the limitations associated with generalizing autopsy studies from one nation, with much of Africa (including Zambia) identified as "high risk" on the Infectious Disease Vulnerability Index, it is not improbable the aforementioned testing percentages reflect reality in many African nations [23]. Under this assumption, we multiplied 15.9% and 32% by each African nation's estimated all-cause mortality in 2020 and 2021, respectively, to obtain expected number of year-end deaths with COVID-19 (Supplementary Figure 1) [16, 17]. These expectations were then divided by infection fatality ratios (IFRs) – a comparison of infections and deaths due to infection – obtained using parametric methods from Sorensen et al. (2022) and Onovo et al. (2021) at multiple pandemic time points [24, 25]. The result is the expected number of year-end COVID-19 infections (Figure 2, Supplementary Figure 2), which can be compared to reported cumulative COVID-19 cases in 2020 and 2021 to produce another set of multiplicative factors (Figure 3) that expand the range of credible infection estimates.

When discussing these data, we intentionally note "deaths with COVID-19" instead of "deaths from COVID-19" because inferring causality is a challenge in postmortem surveillance, although the United States Centers for Disease Control and Prevention (CDC) have issued guidance that COVID-19 should be assumed the underlying cause of death if SARS-CoV-2 is detected [26].

Results

Serology Multiplicative Factors

The available serosurveys yield multiplicative factors illustrative of systematic underdetection and underreporting (Figure 1). Multiplicative factors ranged from 2 (Cape Verde, July 2020) to 3,795 (Malawi, June 2020), implying that 1 in 2 and 1 in 3,795 infections were respectively detected in these nations early in the pandemic. Notably, nearly half the multiplicative factors were of hundreds-order-of-magnitude, facilitating discernment of 4 distinct COVID-19 waves previously obscured by low amplitude peaks of confirmed cases (Figure 1) [22].

Kenya, for which the largest number of national-level serosurveys were available (6, spanning April 2020 to September 2021), produced multiplicative factors ranging from 630 in May 2020 to 110 in December 2020. This observation of declining multiplicative factors as the pandemic progressed is echoed in data for Malawi, Ghana, Ethiopia, and South Africa.

Inter-Method Comparison: Estimates of Infection

Figure 2 provides an inter-method comparison of estimated infections (per 100,000 population). For many nations, the upper bound estimate of COVID-19 infection burden was produced by the gold estimator, which couples postmortem surveillance data with IFR data from Onovo et al. (2021). The magnitude of these estimates is less likely a byproduct of the timing of the IFR estimates (May 2020) and more likely a byproduct of differences in IFR estimation methodologies, as the [even earlier] April 2020 IFR estimates from Sorensen et al. (2022) generated infection estimates predominantly smaller by several factors.

The lower-bound estimate of COVID-19 infection burden was produced by the estimator shown in blue (serosurveillance data). Additionally, infection estimates for most nations cluster

around 100,000 infections per 100,000 population, signaling that most individuals may have already experienced infection at least once.

Inter-Method Comparison: Multiplicative Factors

All African nations yielded multiplicative factors exceeding 1 for both surveillance methods (Figure 3), indicative of divergence between "ground truth" infections and reported cases. Also notable in Figure 3 is concordance among multiplicative factors calculated using IFRs from Sorensen et al. (2022), observable in the clustering of red-shaded markers. Of these, the purple (April 2020 IFRs) and maroon marker (January 2021 IFRs) corresponded to the smallest and largest multiplicative factors, respectively.

Multiple North African nations (Tunisia, Morocco, Libya), island nations (Cape Verde, Seychelles), Botswana, and South Africa yielded small multiplicative factors (<20). Interestingly, South Africa's established indicator- and event-based disease surveillance system and Cape Verde's and Seychelles' geographic isolation contrasts with weakened public health infrastructure in North Africa, where nations have grappled with a paucity of resources to adequately chronicle COVID-19 [27].

Finally, the change in x-axis scale from Figure 3 (a) to (b) also reveals an order-of-magnitude decrease in multiplicative factors from 2020 to 2021, perhaps coincident with improved testing infrastructure and implementation of interventions.

Assessment of Vulnerabilities

One explanation for underascertainment is tied to health, economic, and social vulnerabilities, the analysis of which Lewis et al. (2022) describe as an unmet need [6, 28]. To assess these vulnerabilities, we explored Surgo Ventures' Africa COVID-19 Community

Vulnerability Index (CCVI) [29]. Across and within 756 regions in 48 African nations, CCVI encodes 7 dimensions of vulnerability (age, epidemiology, fragility, health system, population density, socioeconomics, and transport and housing availability), which can contribute to attenuation of disease signal. We limit our focus to epidemiological factors and health system factors.

In Supplementary Figure 3, we ranked African nations by variance in their respective multiplicative factors and compared this to nation-specific health system, epidemiological, and overall vulnerabilities. South Africa, for example, exhibited not only low variance in its multiplicative factor estimates but also low health system vulnerability, the combination of which may reflect more robust surveillance infrastructure.

Calculating the Spearman Rank correlation between the ascending variances for 2020 and the correspondingly ordered health system vulnerability index values yields a coefficient of 0.44 and p-value of 0.001. At a prespecified α-level of 0.05, we reject the null hypothesis that health system vulnerability and variability in infection estimates are uncorrelated. While this comparison does not establish a definitive relationship, on average, nations with lower inter-method variances have a lower degree of vulnerability compared to nations with higher inter-method variances.

Discussion

Although underascertainment of COVID-19 remains a global challenge, the degree of underdetection and underreporting in Africa appears higher than in other continents. By comparison, multiplicative factors were previously estimated to be between 5 and 50 in North America [30, 31]. Both serosurveillance- and postmortem surveillance-based estimates we

present here suggest COVID-19 infections are tens- to hundreds-fold greater than reported in Africa.

Our process is complementary to a preprinted (not yet peer-reviewed) meta-analysis from Lewis et al. (2022), which also quantifies divergence between seroprevalence-derived infections and reported cases in Africa [6]. However, the meta-analysis relied predominantly on local-level serosurveys primarily obtained in urban settings for inference. In contrast, the national-level serosurveys we leverage, which we also do not restrict to those strictly aligned with the WHO's SEROPREV protocol, are intended to increase generalizability of results [32].

We additionally do not limit the scope of analysis to serosurveillance data in validating our results with postmortem surveillance data, which has the added advantage of facilitating direct estimation of COVID-19-attributable deaths [33]. As Mwananyanda et al. (2021) and Gill et al. (2022) show, in Lusaka, Zambia, fewer than 10% of those who died with COVID-19 were tested for prior to death, an underascertainment in mortality that also extends globally [19, 33]. Supplementary Figure 1 captures this underreporting and underdetection of deaths, comparing reported COVID-19-attributable deaths in 2020 and 2021 to Zambia- and excess mortality-based deaths estimates [34]. Although several nations exhibit negative excess mortalities (e.g., Seychelles), which would suggest that COVID-19 precipitated a reduction in deaths, inflection points in the epidemic curves at the time of first-recorded COVID-19 deaths illustrates there was instead an existing negative trend in all-cause mortality that COVID-19 reversed [35].

The results from our multiplicative framework are concordant with other methods. For example, a stochastic compartmental model for South Africa in a preprinted (not yet peer-reviewed) analysis from Gozzi et al. (2022) suggests South Africa's surveillance system could detect 1 in 16 infections between May 2021 and November 2021, compared to our estimates of 1

in 10 to 20 infections for the same timeframe [36]. Additionally, using a global metapopulation epidemic model, Davis et al. (2021) recovered infection attack rates around 1% for several African nations early in the pandemic, further underscoring discrepancies between reported cases and true infections [31].

One limitation of our approach is that the magnitude of serosurvey-derived multiplicative factors may be associated with serosurvey-specific risk of bias. Supplementary Figure 4 explores this association in stratifying serosurveys by bias risk, as measured by the Joanna Briggs Institute Checklist for Prevalence Studies (JBI). JBI is a validated critical appraisal tool encompassing 9 dimensions of assessment, which SeroTracker uses to classify serosurveys [14, 15]. We find that although the "high bias" stratum corresponded to the highest median multiplicative factor (161) and smallest dispersion compared to the "low bias" and "medium bias" strata (128 and 110), this difference is qualitative, suggesting larger multiplicative factors may not be any more biased than smaller multiplicative factors. Furthermore, propensity for bias does not translate to direction of bias: simply because a serosurvey is classified as biased does not indicate that seroprevalence is lower or higher than true prevalence. Therefore, we cannot establish that higher multiplicative factors stem from higher bias.

A different bias associated with serosurveillance relates to origins of seropositivity, specifically differentiating between vaccine- and infection-induced seropositivity. This is less likely a concern given the low COVID-19 vaccination rate (10%) in Africa for the 2020 – 2021 period of analysis [13]. Even so, about one third of tests chronicled by SeroTracker measure IgG (about half are anti-S), one third measure IgM and IgG, and one third measure total antibody [14]. Additionally, we do not explicitly account for waning immunity and resulting reinfection, which may contribute to certain nations exhibiting infection estimates exceeding the total

population (i.e., any points in Figure 2 and Supplementary Figure 2 exceeding 100,000 cases per 100,000 population). Relatedly, we cannot rule out underestimation of "ground truth" disease burden due to lags between time of infection and time of seropositivity, coupled with seroreversion – the phenomenon in which antibody levels decline to a level below the cutoff for seropositivity [37]. Especially during exponential growth in infections, the effect of this underestimation will be magnified, which would reinforce the role of multiplicative factors as lower bounds for burden of disease.

Another important feature of serosurveys is the populations sampled, which often include healthcare workers, blood donors, and the elderly – all of whom may be differentially exposed to SARS-CoV-2. Our analysis does not consider these characteristics of the sample frame and may therefore overestimate cumulative incidence of COVID-19. In Malawi, for example, the thousands-order-of-magnitude for the June 2020 multiplicative factor could be not only attributable to the nation's status as one of the poorest in Africa but also to an especially unrepresentative sample of healthcare workers and caregivers [38]. Given the scarcity of reported infections stratified on serum donor profiles, mitigating this bias could entail extrapolation of seroprevalence to the general population using weights accounting for demographic differences. The CDC recently published such a reweighting protocol specific to blood donors [39]. An alternative could include assessing intra-nation variability of serology estimates, as nations like Cameroon and South Africa have started releasing local-level serosurveys to the public, and to employ these estimates in a sensitivity analysis for multiplicative factor heterogeneity [40].

An added consideration for contextualizing our results is that our methods combine multiple timeframes to create time-invariant multiplicative factors. Serosurveillance studies from

SeroTracker cover multiple dates from June 2020 – November 2021, whereas postmortem surveillance studies reflect either June – October 2020 or January – July 2021. It follows that multiplicative factors estimated from early pandemic stages may not be as representative of disease dynamics seen in later pandemic stages due to SARS-CoV-2 strain-specific effects. However, the cross-sectional nature of serosurveys suggests that cumulative estimates of infection, such as those presented in our analysis, may be more reliable than conversions to weekly estimates of infection.

Finally, in calculating the estimated number of infections using serosurveillance and postmortem surveillance data, we employed 2020 and 2021 national population size estimates from the World Bank and the United Nations [16, 17]. These estimates were the result of projections prior to the COVID-19 pandemic, which would have the effect of overestimating population size due to unaccounted-for deaths. To quantify the impact of this compounding uncertainty, we performed a sensitivity analysis for 2021 infections and deaths by subtracting the number of COVID-19-attributable deaths in 2020 from the projected population size in 2021. The percent difference between unadjusted infections and adjusted infections was <0.5% for all African nations (Supplementary Table 1), implying that unadjusted projected population sizes are sufficient for analysis.

Asymptomatic infections and variable rates of testing for COVID-19 in Africa, as well as globally, have made it particularly challenging to ascertain the true burden of the pandemic from data, as reflected in the range of multiplicative factors from our analysis and imperfections individually inherent in serosurveillance and postmortem surveillance data [41, 42]. While previous studies have sought to estimate this systematic underascertainment in resource-limited settings, they have relied on a single data stream to make inferences. The innovation of our

approach lies in leveraging not only serosurveillance data (antibody testing) but also postmortem surveillance data (PCR testing) to characterize COVID-19 in Africa. Concordance between these methods, when taken together with other sources of epidemiological data (e.g., syndromic and digital surveillance) to mitigate biases associated with individual data sources, can be leveraged in 2 ways: (1) to help inform allocation of resources to areas exhibiting noticeable divergence in reported infections and recalibrated infections; and (2) to help inform initiatives that can bolster surveillance infrastructure [19, 43].

NOTES

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Potential Conflicts of Interest

NEK reports occasional consulting for Abata Therapeutics in an unrelated field. DS reports previous employment at Pfizer Vaccines (until September 2021) and current employment at Hillevax Inc., as well as occasional consulting (until March 2022) through companies as Guidepoint, GLG, and Third Bridge; DS also reports Pfizer Inc. and Hillevax Inc. stock options. CV reports an Elsevier contract for an editor-in-chief role with the journal “Epidemics”. ML

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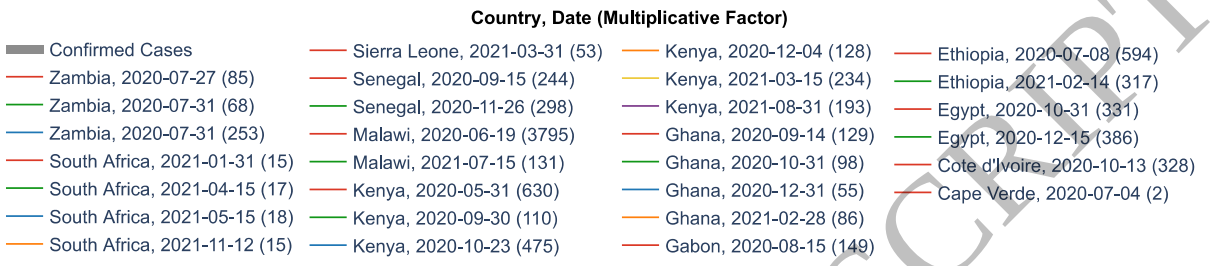
Figure Legends

Figure 1: Confirmed COVID-19 Cases and Serology-Based Infection Estimates for 12 African nations



Reported COVID-19 cases (gray) versus seroprevalence-derived COVID-19 infections (red, green, blue, orange, yellow, purple) per 100,000 population for 12 African nations. Each non-gray curve is created through scaling the corresponding gray curve by a multiplicative factor, parenthetically indicated in the legend, with scaling performed to the nearest half-year to reduce overextrapolation of results. Color order corresponds to chronological temporal order (red: earliest, purple: latest) of serosurvey. Vertical dotted lines represent the last date of each serosurvey sampling period.

Figure 2: Estimated COVID-19 Infections Using Serosurveillance and Postmortem Surveillance in Africa

Comparison of reported COVID-19 cases, cumulative seroprevalence-derived COVID-19 infections (available for 12 nations), and cumulative postmortem-derived COVID-19 infections (Onovo et al. [2021] available for 44 nations, Sorensen et al. [2022] available for 54 nations) per 100,000 population in Africa. The solid black line in each subplot represents 100,000 infections per 100,000 population, implying that an entire population has been infected. ***(a)*** *represents infection estimates through December 31, 2020, and it draws from serosurveys taken between July 1, 2020 and December 31, 2020 as well as from postmortem surveys detailed in Mwananyanda et al. (2021) to derive Zambia-based COVID-19 deaths.* ***(b)*** *represents infection estimates through December 31, 2021, and it draws from serosurveys taken between July 1, 2021 and December 31, 2021 as well as from postmortem surveys detailed in Gill et al. (2022) to derive Zambia-based COVID-19 deaths.*

Figure 3: Multiplicative Factors Needed to Estimate True Infections from Confirmed Cases of COVID-19 in Africa

Comparison of multiplicative factors summarizing ratio of seroprevalence-derived COVID-19 infections (available for 12 nations) and postmortem-derived COVID-19 infections (Onovo et al. [2021] available for 44 nations, Sorensen et al. [2022] available for 54 nations) to reported cases in Africa. ***(a)*** *represents ratio estimates through December 31, 2020, and it leverages postmortem surveys detailed in Mwananyanda et al. (2021) to derive Zambia-based COVID-19 deaths.* ***(b)*** *represents ratio estimates through December 31, 2021, and it leverages postmortem surveys detailed in Gill et al. (2022) to derive Zambia-based COVID-19 deaths.*

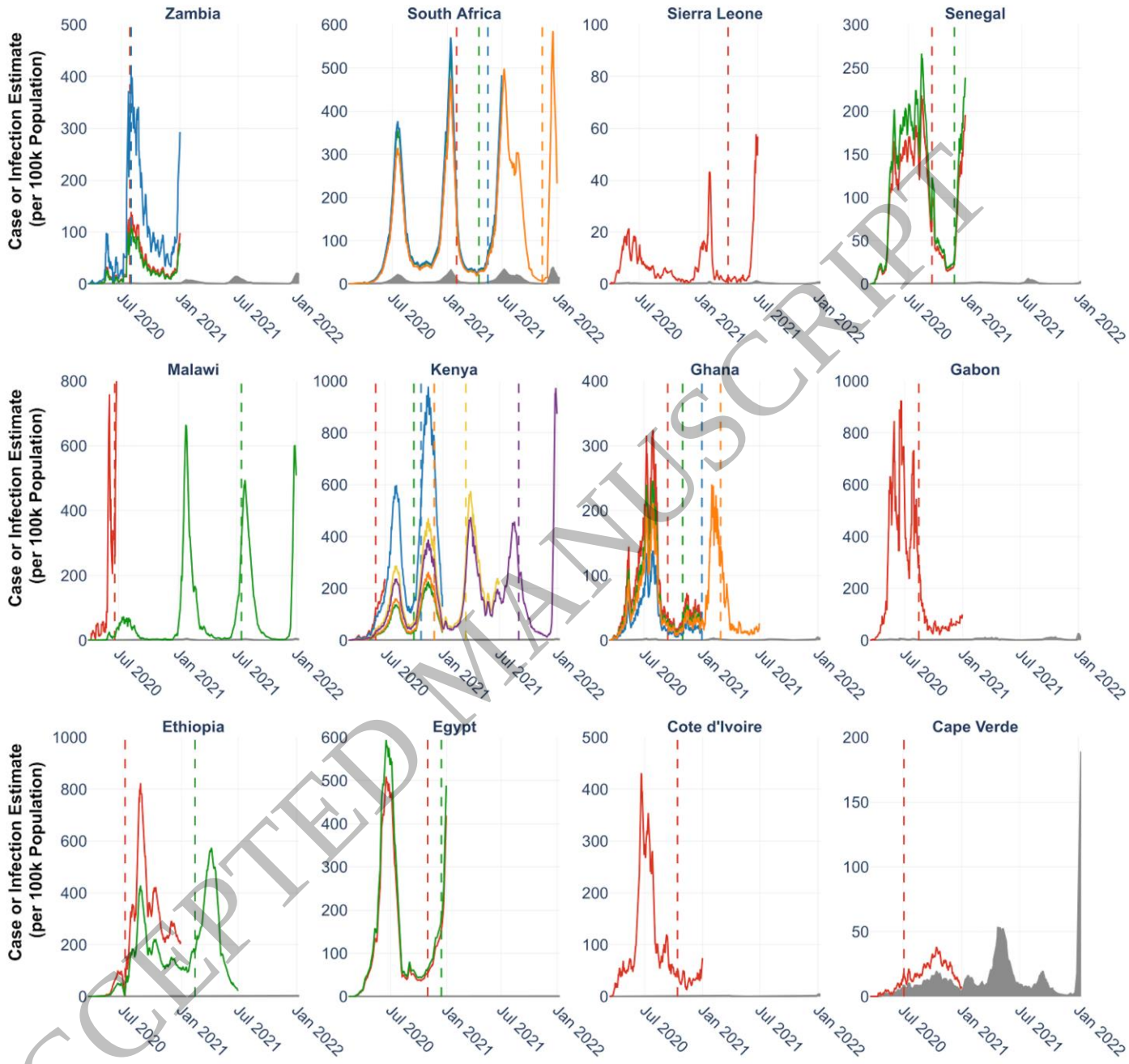


Figure 1
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Figure 2
295x266 mm (x DPI)

Figure 3
295x266 mm (x DPI)