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## **Spatial and spatio-temporal epidemiological approaches to inform COVID-19 surveillance and control: a systematic review of statistical and modelling methods in Africa**

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# BMJ Open Spatial and spatio-temporal epidemiological approaches to inform COVID-19 surveillance and control: a systematic review of statistical and modelling methods in Africa

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## ABSTRACT

**Objective** Various studies have been published to better understand the underlying spatial and temporal dynamics of COVID-19. This review sought to identify different spatial and spatio-temporal modelling methods that have been applied to COVID-19 and examine influential covariates that have been reportedly associated with its risk in Africa.

**Design** Systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

**Data sources** Thematically mined keywords were used to identify refereed studies conducted between January 2020 and February 2022 from the following databases: PubMed, Scopus, MEDLINE via Proquest, CINHAL via EBSCOhost and Coronavirus Research Database via ProQuest. A manual search through the reference list of studies was also conducted.

**Eligibility criteria for selecting studies** Peer-reviewed studies that demonstrated the application of spatial and temporal approaches to COVID-19 outcomes.

**Data extraction and synthesis** A standardised extraction form based on critical appraisal and data extraction for systematic reviews of prediction modelling studies checklist was used to extract the meta-data of the included studies. A validated scoring criterion was used to assess studies based on their methodological relevance and quality.

**Results** Among 2065 hits in five databases, title and abstract screening yielded 827 studies of which 22 were synthesised and qualitatively analysed. The most common socioeconomic variable was population density. HIV prevalence was the most common epidemiological indicator, while temperature was the most common environmental indicator. Thirteen studies (59%) implemented diverse formulations of spatial and spatio-temporal models incorporating unmeasured factors of COVID-19 and the subtle influence of time and space. Cluster analyses were used across seven studies (32%) to explore COVID-19 variation and determine whether observed patterns were random.

**Conclusion** COVID-19 modelling in Africa is still in its infancy, and a range of spatial and spatio-temporal methods have been employed across diverse settings.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The review adopted the reporting guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
- ⇒ The review will improve our understanding of the current state of COVID-19 spatial and spatio-temporal modelling in Africa.
- ⇒ Selection of studies and extraction of data was done by a multidisciplinary team with expertise in spatial modelling, COVID-19 and conducting systematic reviews.
- ⇒ The review may have missed relevant studies or models implemented in practice but not described in the current literature.
- ⇒ This review could be limited by studies that reported insufficient modelling details.

Strengthening routine data systems remains critical for generating estimates and understanding factors that drive spatial variation in vulnerable populations and temporal variation in pandemic progression.

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## INTRODUCTION

The rapid and devastating spread of COVID-19 pandemic, caused by the novel and SARS-CoV-2 pathogen, was first discovered in Wuhan, Hubei Province, China, in the latter part of 2019. In Africa, the first case was reported on 14 February 2020 in Egypt. The virus's differential spread and impact across Africa have led to approximately 9 million cases and resulted in 172 301 deaths as of 3 June 2022.<sup>1</sup> Its spread across and within countries in sub-Saharan Africa (SSA) has not followed homogenous patterns due to the global vaccine inequity, increasingly severe infection waves of the pandemic and vulnerable health and economic systems.<sup>2,3</sup> Furthermore, its interaction with HIV, tuberculosis,



malaria and non-communicable diseases has affected its clinical presentation, treatment response and severity. This interaction has hampered control efforts and led to adverse outcomes, consequently threatening the achievement of the development goals encapsulated in the African Union's Agenda 2063: The Africa We Want and the United Nation's Sustainable Development Goals.<sup>4</sup>

Concerningly, severe outcomes attributed to COVID-19 infection in SSA have been exacerbated by the scarcity of critical care resources, grossly underfunded and inadequate healthcare facilities, and insufficient training of healthcare workers.<sup>5</sup> To mitigate the impact of health service disruptions the African Union initiatives, such as the Partnership to Accelerate COVID-19 Testing in Africa, have sought to secure diagnostics targeting the vulnerable and underserved segments of society. The African Medical Supplies Platform and the African Vaccine Acquisition Task Team made it possible for member states to jointly secure crucial medical supplies and vaccines.<sup>6</sup> Despite these initiatives, the burden remains high due to inequalities in vaccine access and roll-out in individual countries. This inequality is partly due to infrastructural and capacity limitations, which have impacted individual countries' ability to detect, assess, notify and respond to the pandemic.

Previously, in the early phase of the pandemic, disease modellers had projected up to 70 million cases and approximately 3 million deaths in Africa by June 2020.<sup>7</sup> This did not happen, and several hypotheses have been presented to explain the unique transmission dynamics resulting in fewer cases and deaths being reported. These include the area's young population, climatic diversity, pre-existing immunity and genetic factors.<sup>8</sup> However, concerns have been raised about the reliability of the data used to quantify the burden due to limited surveillance capacity, possibly leading to suboptimal case detection and incomplete documentation of COVID-19 cases, deaths, hospitalisations and vaccinations across the continuum of care.<sup>9</sup>

Despite data quality limitations, epidemiological surveillance continues to be an essential intervention for combating COVID-19 in 2022. Different modelling approaches have been employed to comprehend the COVID-19 burden quantitatively, particularly in areas where variants are evolving. In local transmission settings, there is an urgent need to understand the relative importance of diverse and complex socioeconomic, cultural and contextual factors impacting COVID-19 endemicity. An enhanced computational ability has created an ideal environment for the upsurge of diverse models characterising the dynamic patterns of COVID-19 in space and time. However, model estimates are yet to be fully embraced, given the substantial uncertainty and diverging methodologies employed. Additionally, the utility data from diverse sources within different modelling frameworks have resulted in inferential differences. This discrepancy has made it difficult to target the limited resources to the most vulnerable populations.

As more transmissible variants continue to spread across SSA, driven in part by limited adherence to prevention measures and global distribution inequalities, spatial modelling of COVID-19 at relevant thresholds remains critical. It is essential to track COVID-19 spread within the population and assess the impact of interventions for an effective and sustainable response. In the era of evidence-based decision-making, it is imperative to understand spatial methods and identify context-specific risk factors in a resource-constrained setting. By describing important methodological specificities, our review provides a decisive perspective with the potential to improve the framework for modelling COVID-19 in Africa.

## METHODS

The review adopted the reporting guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.<sup>10</sup>

### Search strategy

The search for studies in various bibliographic databases was guided by an information specialist at the College of William & Mary with substantial experience conducting systematic reviews. Thematically mined keywords were iteratively funnelled using Boolean operators and truncations before being deployed across databases as outlined in the search strategy (online supplemental table 1). A manual search was also done through the reference lists of the included studies. Google Scholar was also used to search for additional publications that might have been missed. The final search was conducted in February 2022 and was limited to studies conducted between 30 January 2020 and February 2022. The starting date corresponded to the date the WHO declared COVID-19 a public health emergency of international concern.<sup>11</sup> Relevant studies were imported into Refworks—a web-based bibliography and database manager.

### Study selection

Two authors (NPR and LT) independently screened studies based on the information contained in their title and abstract. Here the primary focus was to identify peer-reviewed articles that demonstrated the application of spatial and temporal approaches to COVID-19 outcomes.

The second stage was more stringent, with all the authors screening the full text of the eligible studies. Studies were assessed based on their availability, their publication language and the methodological merit of their spatial or spatio-temporal approaches. Discrepancies were resolved by consensus.

Studies that did not comply with these criteria were excluded from further review. Examples of exclusions included articles written in a language other than English, articles that were not peer-reviewed (e.g. letters, editorials), studies that did not focus on COVID-19 outcomes, and studies that did not use spatial or spatio-temporal approaches. Grey literature such as commentaries, reports

and expert reviews that did not include original research was read and relevant studies were cited. In order to be as inclusive as possible, when necessary, corresponding authors were contacted for the full text and additional modelling information.

### Data extraction

A standardised extraction form based on the CHARMS (critical appraisal and data extraction for systematic reviews of prediction modelling studies)<sup>12</sup> checklist was used by three authors (JNO, NPR and LT), to extract the meta-data of the included studies. Extraction discrepancies among the authors were resolved by consensus and by an independent arbitrator (CD). The bibliographic information, study objective, covariates, analytic methods and key findings were extracted from each study (online supplemental table 2).

### Quality appraisal

The studies selected had profound heterogeneity in their modelling approaches, data sources and COVID-19 outcomes. Thus, a validated quality assessment tool with 8-point scoring criteria was used to appraise individual studies based on their methodological rigour.<sup>13 14</sup> Screening questions based on the criteria were used to assess the overall quality of the individual studies and sort them into four categories, namely, very high (>13), high (11–13), medium (8–10) and low (<8) (online supplemental table 3).

### Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this review.

## RESULTS

### Literature search

The flow chart for the search process is given in [figure 1](#). During the search process, 2065 studies were identified from the database searches and 13 studies from sources not detected by our search. After the removal of duplicates, the authors screened 827 articles by reading their titles and abstracts. Of these, 31 full texts were reviewed, which resulted in 22 studies that met the inclusion criteria. Individual study characteristics are summarised in online supplemental table 4.

### Time intervals and scale of analysis

The geographical scale and scope of studies varied across SSA. Thirteen studies (59%) were published in 2021, eight (36%) were published in 2020 and one was published in 2022. The most prolonged study period was 12 months (1 year), while the shortest period was 4 days. Overall, the average study duration was 4 months. Spatial analyses were generally conducted over administrative units, but the aggregation scale differed markedly. Twelve studies (55%) were done in individual countries, whereas 10 studies (45%) were jointly done across countries.

### Data sources and measures of COVID-19 outcomes

Open access to global, continental and national repositories provided a rich source of COVID-19 data and covariates. The Africa Centres for Disease Control and Prevention, the WHO situation reports, and Johns Hopkins University's Coronavirus Resource Center, used in 10 studies (45%), provided metrics for tracking COVID-19 cases and mortality. Ten studies (45%) used in-country health information systems to report cases, mortality and vaccination trends. Previously conducted geographically referenced surveys provided useful demographic and socioeconomic indicators used in two studies (9%).

Different metrics were used to quantify the burden of COVID-19 in space and time, with some studies leveraging more than one outcome. Reported cases (daily, monthly, confirmed) were used in 18 studies (82%), and mortality rate was used in two studies (9%). Other measures were COVID-19 vulnerability index, used in two studies (9%), and vaccination coverage, used in one study (4%) ([table 1](#)).

### Covariates

[Table 1](#) shows a broad suite of indicators/covariates used across studies. These were categorised into six leading indicators: socioeconomic, demographic, geographic, epidemiological, environmental and behavioural. The most common socioeconomic variable was population density, while the proportion elderly population (above 65 years) was the most common demographic variable. HIV prevalence was the most common epidemiological indicator. Temperature was the most common environmental covariate, whereas cigarette smoking was the most common behavioural indicator used to understand the population's vulnerability to COVID-19.

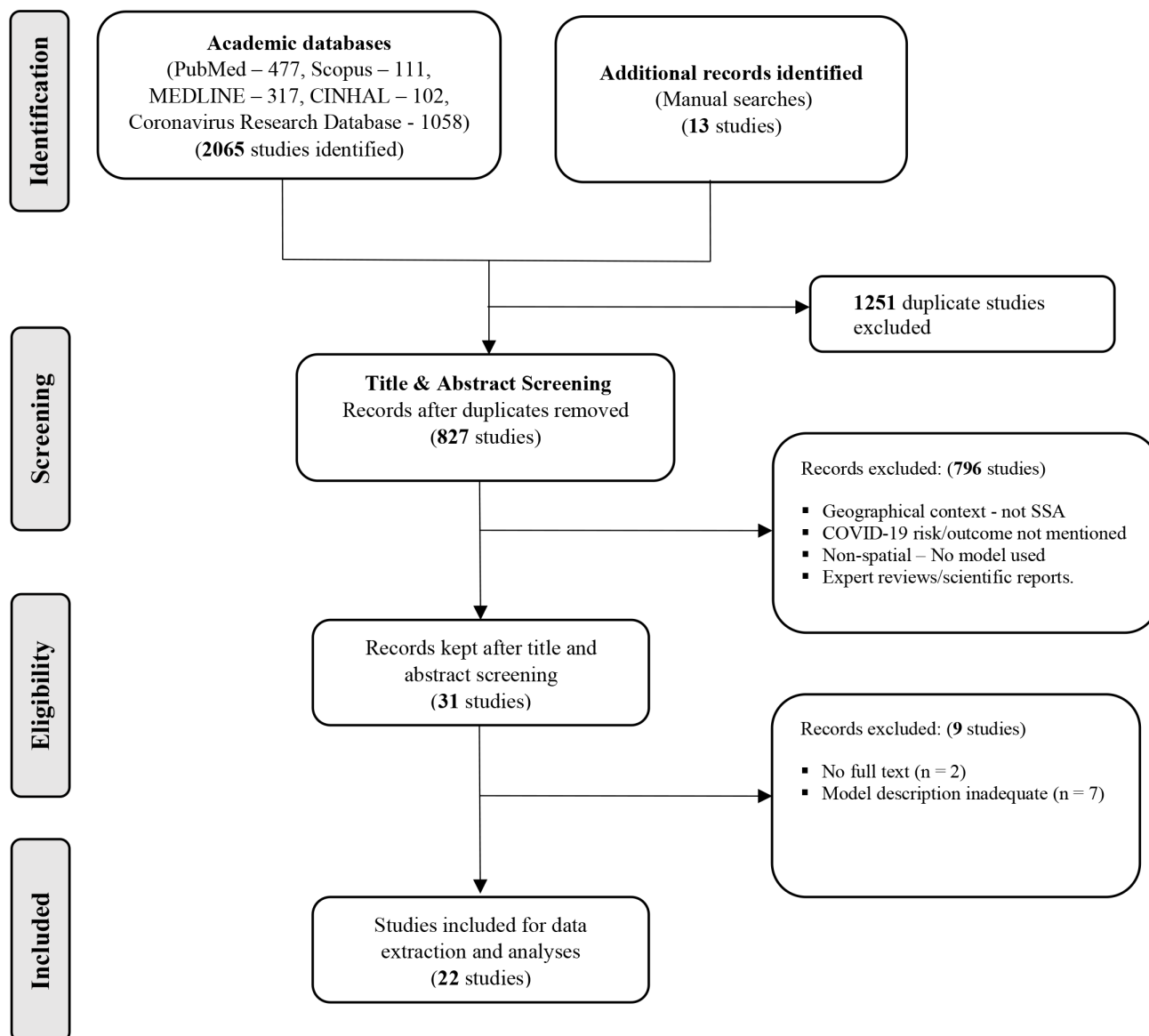
### Data pre-processing

More than half of the articles acknowledged the uncertainty about the accuracy of COVID-19 data due to inconsistencies across testing, reporting and data availability. Thus, pre-processing procedures such as data cleaning, transformation and reduction were undertaken to optimise the model's predictive ability. To determine the relevance between COVID-19 outcomes and baseline covariates, correlation analyses were undertaken for seven studies (32%).<sup>15–21</sup> A higher degree of multicollinearity can result in the standard errors for the coefficients getting inflated; therefore, a variety of data transformation techniques were employed to make the data more suitable for modelling. These included procedures such as standardisation of continuous covariates using the z-transform<sup>15 22 23</sup> and logarithmic transformation of variables that were not normally distributed.<sup>15 23</sup> In two studies, georeferenced data were resampled at appropriate spatial resolutions,<sup>23 24</sup> for example, 1 km by 1 km spatial resolution ([table 2](#)).

### Analytical approaches

[Table 3](#) shows the various spatial, temporal and spatio-temporal methods that were used to visualise patterns,





**Figure 1** Flow diagram for the study selection process. All the references retrieved from the database query were manually assigned to one exclusion category or passed to the next step. SSA, sub-Saharan Africa.

explore spatial clusters, and model risk across space and time. Some studies did not explicitly report the utility of these methods, but their reported results implied the use of these methods.

Before implementing statistical models to explore COVID-19 outcomes, visualisation of various COVID-19 outcomes was conducted. These visualisations provided an ideal environment for understanding the distribution of COVID-19 over space and time. Data visualisation, used by 16 studies (73%), was the most consistent method used by all the studies to present the distribution of COVID-19. Cluster analyses were used to explore COVID-19 outcomes that varied over space and time and determine whether observed patterns were due to chance. Various approaches were used in six studies (27%) to measure and test for spatial autocorrelation. Four studies used the global Moran's I index to determine the clustering patterns.<sup>17 18 23 25</sup> Two studies used hot spot analysis to

identify the location with the highest incidence. Specifically, the Getis-Ord  $G_i^*$  ( $G_i^*$ ) statistic for each class of COVID-19 case intensity represented the z-score, with higher positive z-values being considered hot spots while smaller and negative z-values were taken as insignificant and thus discarded.<sup>15 25</sup> Other measures included the Anselin local Moran's I and Kulldorff's space-time scan, which was used to assess the temporal, spatial, and space-time community clusters of COVID-19 at the infra-national scale.<sup>25 26</sup>

To illuminate important relationships between COVID-19 and the relevant population-level metrics, diverse studies explicitly employed statistical modelling frameworks. Three independent studies used multiple formulations of spatial-temporal conditional autoregressive models implemented within a Bayesian framework incorporating unmeasured factors of COVID-19 and the subtle influence of time and space. Specifically,

**Table 1** COVID-19 indicators and covariates

Indicator	Covariates	Number
Socioeconomic	Population density <sup>15–18 22 31 41–43</sup>	10
	Household characteristics <sup>17 22 41 43</sup>	4
	Wealth index <sup>18 23 41</sup>	3
	Employment rate <sup>22 31</sup>	2
Demographic	Elderly population (above 65 years) <sup>17 18 22 23 31 41 43–45</sup>	9
	Age <sup>24 42 44</sup>	3
	Sex <sup>23 24 44</sup>	3
Geographic	Travel time to health facility <sup>22 24 31 46</sup>	4
	Distance to roads <sup>16 23 46</sup>	3
	Urbanisation <sup>31 46</sup>	2
Epidemiological	HIV prevalence <sup>16 17 22 31 41 42</sup>	6
	Tuberculosis <sup>23 41</sup>	2
	Cardiovascular fatality <sup>17 23</sup>	2
	Asthma prevalence <sup>17</sup>	1
	Diabetes prevalence <sup>23 31</sup>	2
	Hypertension prevalence <sup>23 31</sup>	2
	Obesity prevalence <sup>23 31</sup>	2
	Malnutrition <sup>31</sup>	1
	Noncommunicable diseases <sup>42</sup>	1
	Under 5 mortality <sup>15</sup>	1
	No. of hospital beds <sup>19 22 23 31</sup>	4
	No. of doctors <sup>19</sup>	1
	Behavioural	Cigarette smoking <sup>17 23 30 31</sup>
Khat chewing <sup>23</sup>		1
Alcohol consumption <sup>23</sup>		1
Cooking inside the household <sup>23</sup>		1
Environmental	Temperature <sup>16 20 23 42</sup>	4
	Wind speed <sup>20 23</sup>	2
	Relative humidity <sup>20 23</sup>	2
	Elevation/slope <sup>16</sup>	1
	Precipitation <sup>16 23</sup>	2
	Solar radiation <sup>23</sup>	1

**Table 2** Data pre-processing

Process	Number
Collinearity statistics	7
▶ Spearman rank correlation <sup>18 20</sup>	
▶ Pearson's correlation <sup>15–17 19</sup>	
▶ Non-parametric tests <sup>21</sup>	
Variable transformation	3
▶ Standardisation <sup>15 22 23</sup>	
▶ Normalisation <sup>15 23</sup>	
Resampling to relevant spatial and temporal resolution <sup>23 24</sup>	2

a discrete spatial binomial regression model was used to model vaccination coverage subnationally, and semi-parametric spatial-temporal models were used to model the monthly confirmed COVID-19 cases.<sup>21 27 28</sup> Spatial regression models were also used to model spatial dependent data. In one study, the spatial lag, spatial error and spatial autoregressive conditions models were used to model COVID-19 prevalence data.<sup>18</sup> The generalised method of moment's model that was used to explore COVID-19 confirmed cases and attributable deaths,<sup>29</sup> a 2-component hurdle Poisson based on a framework of distributional regression, was used to relate COVID-19 cases to spatial and spatio-temporal covariates in Africa.<sup>19</sup>

**Table 3** Analytical methods used in studies

Category	Method	Number
Visualisation	Risk map	16
	▶ Transmission <sup>22 43</sup>	
	▶ Exposure <sup>22</sup>	
	▶ Vulnerability <sup>31 45 46</sup>	
Rate map	▶ Cases <sup>15 16 20 25 26 29 30 41 44</sup>	7
	▶ Mortality <sup>17</sup>	
	Balloon and area charts <sup>47</sup>	
Cluster analysis	Spatial autocorrelation	7
	▶ Global Moran's I <sup>17 18 23 25</sup>	
	Hotspot analysis	
	▶ Getis Ord statistic <sup>15 25</sup>	
▶ Anselin local Moran's I <sup>25</sup>		
Kulldorff's space-time scan statistical analysis <sup>26</sup>		
Spatial/spatio-temporal analysis	Spatial regression models <sup>18</sup>	13
	Bayesian conditional autoregressive models <sup>21 24 43</sup>	
	2-component hurdle Poisson <sup>19</sup>	
	Generalised additive model <sup>20</sup>	
	Temporal trends <sup>15 18 25 26 30 42 44 47</sup>	

To accommodate the cumulative lag effect of climatic covariates on COVID-19 cases, one study used general additive modelling, a moving average estimation procedure.<sup>30</sup> The geographically weighted regression was used to explore the predictive power of covariates based on their spatial location.<sup>17</sup> In Zambia, a classification tree based on recursive partitioning principle was employed to analyse the factors associated with the COVID-19 cases.<sup>16</sup> Online supplemental table 4 shows the spatial and temporal dependencies employed by various studies.

In order to complement the different modelling approaches, COVID-19 vulnerability assessment was done by three studies to understand COVID-19 risk. This vulnerability assessment entailed combining multiple geospatial and socioeconomic indicators into a single index and mapping its spatial variation.<sup>22 23 31</sup> Different software was used to implement different types of models, with R and ArcGIS being the most commonly used software (online supplemental table 4).

## DISCUSSION

The COVID-19 pandemic has substantially impacted the health, societies and economies of many African countries. Spatial and spatio-temporal approaches have played a critical role in shifting and improving our understanding of the available control and treatment options. However, the uneven burden may be attributed to the diverse data sources, covariates and analytical approaches employed. This research is the first systematic review to comprehensively investigate spatial methods and context-specific risk factors related to COVID-19 modelling in Africa.

The disproportionate effect of COVID-19 within and across countries projects an underlying problem that may

be attributed to the lack of reliable and timely data on which the health system can base its response and mitigate the burden at relevant thresholds. Additionally, a comprehensive surveillance framework and regular seroprevalence surveys, neither of which were available during the peak of COVID-19 infection in most countries, may have underestimated the true impact of the pandemic.<sup>32</sup> However, these differences reveal how essential predictions at lower spatial resolution are and demonstrate the need for robust continental coordination for homogeneous enforcement of policy across countries with varying demographics and diverse systems for health provision. Notably, there is a need to standardise data collection protocols and advance tools that enable seamless integration of clinical data obtained from different sources within the healthcare ecosystem to monitor the trajectory of current and potential variants in the population.

Grossly underfunded healthcare systems have limited many countries' capacity to generate, analyse and interpret COVID-19 related data and its risk factors.<sup>33</sup> This underfunding has led to the uptake modelling scenarios based on incomplete and inaccurate data. However, these estimates remain intractable given an inconsistent assessment of the quantitative impact of important risk factors. Amidst these limitations, understanding the burden of COVID-19 relative to complex socioeconomic, demographic, behavioural, geographic and epidemiological indicators across spatial and temporal scales that make some populations more susceptible is critical for informed decision-making. Studies have shown that socioeconomic indicators such as population density, household characteristics, and wealth have previously influenced transmission dynamics.<sup>34 35</sup> However, data related to the socioeconomic impacts of COVID-19 take time to collect, clean and analyse, and are always at risk of becoming outdated before their release.<sup>36</sup> This may blur the fuller picture of COVID-19's effects on households. More evidence on the extent to which socioeconomic determinants of health such as gender, poverty and discrimination affect the vulnerable population is critical. No model accounted for patient-level characteristics, which might have revealed important unique traits among subgroups. Combining individual and areal covariates in a spatial modelling framework has the potential to enhance inference by reducing ecological fallacy. Future modelling of COVID-19 should explore how individual risk factors can be included in the modelling framework.

The various studies modelled a wide variation of COVID-19 outcomes. However, data on COVID-19 mortality was sparse, which might have led to an underestimation of its true extent. Compared with the global average of 62% reported deaths, only 10% of deaths have previously been reported in Africa. This under-reporting suggests a need to improve the sensitivity and specificity of the COVID-19 mortality data.<sup>37</sup> Furthermore, there is a need to include clinical characteristics with potential prognostic implication even as COVID-19 continues to evolve.

Visualisation of COVID-19 outcomes at different spatial and temporal resolutions and cluster analyses were the most common approaches for understanding the distribution of COVID-19 outcomes for various stakeholders. Patterns observed were highly dependent on the selected spatial scale due to modifiable areal unit problem. For cluster analyses, the general assumption was that COVID-19 cases followed a Poisson distribution with a constant risk profile proportional to the at-risk population. Spatial-only models revealed an underlying spatial variation of COVID-19 attributable to its risk factors, suggesting a need for deeper understanding of covariates in their different contexts as an essential step for discerning potential future scenarios. However, only a few studies explicitly incorporated spatial random effects in their modelling framework. In the context of COVID-19 propagation, spatial dependence between analysis units is highly probable and overlooking the spatial effects within a modelling framework would likely lead to biased results. Few studies reviewed explicitly accounted for the temporal dependence within their modelling framework through autoregressive integrated moving average (ARIMA), random walks or spline functions. Given the complex COVID-19 transmission dynamics, machine learning approaches would be ideal for important spatio-temporal interaction effects.

As more data becomes available, model development and refinement remains vital for understanding COVID-19's infectiousness in local settings. Most importantly, projections of COVID-19 need to be updated to account for mobility patterns on the intrinsic spread of COVID-19, in order to reflect the heterogeneous risk in space and time. As more countries review their policies on travel and border closures to reignite their economies, incorporating mobility data in spatial models will help mitigate the local transmission of COVID-19. The extent of vaccine coverage and the potential effectiveness of different vaccination strategies can also be incorporated within the modelling framework, as previously demonstrated with Ebola and dengue vaccinations.<sup>38 39</sup> In the era of reproducible science,<sup>40</sup> periodically reviewing, validating, and updating spatial models to accommodate new data sources, improved data quality, enhanced computing power and novel methodological approaches will continue to be an essential strand in quantifying the burden of COVID-19.

### Limitations of this review

The review findings should be interpreted cautiously while accounting for the limitations and the gaps in the field. The descriptions of spatial models are based on current publications. We could not evaluate models and establish the appropriate level of confidence in the performance due to the varying modelling frameworks employed by different studies and the limited modelling details provided by studies. Additionally, the methodological choices and covariates used were widely influenced by the data available. Comparison between countries was

also challenging to ascertain due to population sizes and differences in health policies (eg, curfew, testing regimes) that shifted over time. A similar review is necessary when more data and models are published.

### CONCLUSION

Despite the challenges posed by sparse data at the relevant thresholds, the uptake of spatio-temporal models to illuminate the relationship between COVID-19 and its risk factors remains critical for rational decision-making, prioritisation of limited resources and setting national targets. Although not all countries reported COVID-19 statistics at the same frequency and quality, our review has shown a range of methodologies deployed in divergent contexts from January 2020 to February 2022. Overall, we contribute to the growing body of knowledge and methods for quantifying the burden of COVID-19 in Africa. We also highlight the importance of high-quality and timely estimates subnationally and underscore the need for investing in a reliable health information system across the continuum of care, as an imperative towards a more efficient public health response for an evolving and unpredictable virus.

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**Contributors** JNO and CBD conceived and designed the systematic review. JNO, LT, NPR conducted the literature search, study selection and data extraction. JNO wrote the first draft of the manuscript. CBD revised the draft critically for important intellectual content. All authors read and approved the final version of the manuscript. JNO is the guarantor of the study and responsible for the overall content.

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