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Excess mortality during the COVID-19 pandemic in low-income and lower middle-income countries: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction The COVID-19 pandemic has been marked by a massive death toll. However, the overall effect of the pandemic, including potential unintended negative impacts of some control measures, on mortality remains poorly understood in low-income and lower middle-income countries (LLMICs). This review aims to summarise the available literature on excess mortality in LLMICs, focusing on the methods and data sources used in estimating excess mortality and the drivers of excess mortality.

Methods and analysis We will review the available literature and report results in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis. Searches will be conducted in PubMed, Embase, Web of Science, Cochrane Library, Google Scholar and Scopus. All published studies that report on the estimates of excess mortality in populations of LLMICs will be included. This will include those with a publication date from 2019 onwards and those with at least a 1-year non-COVID-19 period as the comparator in the estimation of excess mortality during the pandemic. There will be no language restrictions on the search. The meta-analysis will include studies with extractable data on excess mortality, methods, population size, and observed and expected deaths. We will use the Mantel-Haenszel method to estimate the pooled risk ratio with 95% CIs.

Ethics and dissemination As there is no primary data collection, there is no requirement for ethical review. The results will be disseminated through peer-reviewed journal publication and conference presentations.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review will appraise existing estimates of excess mortality in low-income and lower middle-income countries, assess factors determining excess mortality across different settings and socioeconomic groups, and explore innovative approaches to estimating excess mortality.

⇒ Strengths of the review include a thorough methodology, following guidelines for systematic reviews and meta-analyses, a careful assessment of the quality of included studies according to the Newcastle–Ottawa Scale score and robust methods of meta-analysis.

⇒ Potential limitations of the review include the possibility of a low number of primary studies meeting the criteria for inclusion, large variation in methods of included studies and limited representativeness of findings on account of insufficient studies from some parts of the world.

INTRODUCTION

The coronavirus family comprises hundreds of viruses; however, only six (229E, NL63, OC43, HKU1, SARS-CoV and MERS-CoV) have been reported to cause mild to severe respiratory tract infections in humans.[1] In 2019, SARS-CoV-2, the causal agent of COVID-19, was first identified in Wuhan, China.[2] Despite intensive, wide-scale attempts to contain the disease in China, the virus rapidly spread around the world, and the WHO declared COVID-19 a pandemic in March 2020.[3] Globally, over 6.5 million people have died and more than 623 million have been infected. Almost 9 million cumulative cases have been documented in Africa, and the death toll exceeds to 173 000 people.[4]

Around the world, nations implemented non-pharmaceutical public health interventions to curb the COVID-19 pandemic, such as regulations to restrict movement and contact (lockdowns) and the use of masks to reduce the transmission of the virus.[5–7] Despite the intrinsic potential of these restrictions to lower deaths from COVID-19 and certain non-COVID-19 deaths such as traffic-related deaths,[8 9] these measures may have inadvertently raised the death toll for certain other causes of death, for example, those related to non-communicable diseases or reproductive, newborn and child health.[10] For example, an increase in mortality has been reported among patients with chronic illnesses because some of the lockdown

measures made it more difficult for patients to receive timely medical attention.[10 11] The pandemic response has been shown to have been associated with increased deaths due to the exacerbation of domestic violence, suicide and mental illness.[9 12 13]

Confirmed COVID-19 deaths alone are unlikely to capture the full extent of the pandemic's burden.[14] Excess mortality is a more comprehensive approach to measuring both the direct and indirect impacts of the pandemic on deaths. According to the WHO, excess mortality is 'the mortality above what would be expected based on the non-crisis mortality rate in the population of interest'.[15] It is the difference between the number of deaths that occur during a pandemic and the number of deaths that would have occurred in the absence of the pandemic. Excess mortality includes deaths directly caused by COVID-19 infection, and deaths caused by socioeconomic challenges (such as compromised food security on account of food systems supply chain disruptions and lack of access to medical services) and deaths from other causes (such as conflicts). The estimated excess mortality rate due to the COVID-19 pandemic may be 5-fold to 25-fold higher than reported COVID-19 mortality rates.[14]

In low-income and lower middle-income countries (LLMICs), excess mortality during the COVID-19 pandemic is not well understood,[16–19] also because routine mortality reporting has severe shortcomings due to incomplete vital registration systems.[5 20] Available data are often from selected geographical sites only or inaccurate. Sometimes, multiple data interpolation (applying models to fill the spatial or temporal gaps in reports) and extrapolation (projecting sentinel groups to the general population) have been used to estimate excess mortality.[21]

We plan to explore the tools that have been used to capture and report excess mortality. For instance, satellite imagery to count new graves created during COVID-19 has been applied for the first time for population mortality estimation.[22] Participatory epidemiology was used to gather information from so-called important informants[23] or randomly selected members of the population[24] on changes in the number of deaths in selected areas over a given period.

It is widely accepted that reported cases generally capture only a small portion of total infections, and deaths are mostly undercounted, in particular in LLMICs.[25–27] Shang *et al*[28] reported on global excess mortality and found that the pooled excess mortality in developing countries was higher compared with developed countries, but they did not specifically explore LLMIC results and assess methods and data used in these countries. Therefore, this review aims to provide a more focused and more up-to-date overview of the existing literature on excess mortality in LLMICs. Specifically, its objectives are to (1) summarise the results of existing studies of excess mortality in LLMICs, (2) describe methods and data sources used in estimating excess mortality, and (3) identify the drivers of excess mortality in LLMICs.

Review questions

1. What is the estimated level of excess mortality during the COVID-19 pandemic in LLMICs?
2. What methods and data are used to estimate excess mortality in LLMICs?
3. What are the factors influencing excess mortality in LLMICs?

METHODS AND ANALYSIS

We will review the available literature and report results in line with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA).[29] The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist has been completed and is available in online supplemental file 1.

Database searches

We will search the following electronic bibliographical databases: PubMed, Embase, Web of Science, Cochrane Library, Google Scholar and Scopus.

In addition, we will search the reference lists of included studies of relevant publications. The search strategy will include terms relating to key concepts of the review (1) COVID-19 and/or SARS-CoV-2, (2) excess mortality and (3) LLMICs. Each of these terms will be operationalised with a range of synonyms and adapted for different databases (online supplemental file 2). For Google Scholar, the search strategy will be limited to keywords in titles and abstracts in order to reduce the number of identified titles to a manageable amount.

There will be no language restrictions. The author team speaks English, French and Spanish. Any articles published in languages the authors do not speak and understand will be translated into English using the DeepL platform (https://www.deepl.com/en/translator). The search will be limited to studies published between 2019 and the date the searches are run. The searches will be rerun before the final analyses and further studies will be retrieved for inclusion.

Procedures

The Grading of Recommendations Assessment, Development, and Evaluation framework will be used in this review to assess the quality of evidence and to determine the strength of the available evidence.

To specify the research questions, the 'population, intervention, comparator and outcome' framework has been adopted.

Participants/population

The review will include population-level or cohort studies from LLMICs, independent of the administrative level (district, region, nation) or study design (cohort study design). Facility-based studies will be considered to examine covariates and the methods used, but disease-specific studies will be excluded. All age groups and results for any population group reported in the original studies will be included in the review.

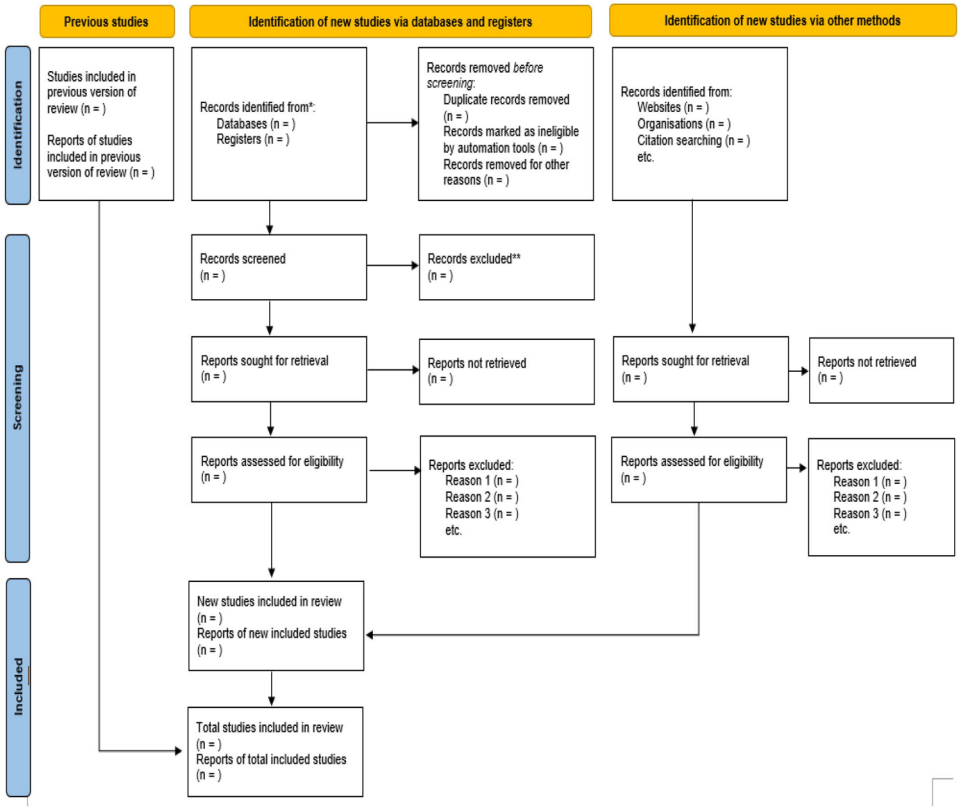

Figure 1 Preferred Reporting Items for Systematic Review and Meta-Analysis 2020 flow diagram template.[29]

Intervention(s)/exposure

The exposure of interest is the COVID-19 pandemic. This refers to the period from when the WHO declared COVID-19 a pandemic on 11 March 2020, to the most current wave of COVID-19 infection that will be reported in the population under review.

Comparator(s)/control

All-cause mortality in the non-COVID-19 period (registered or estimated). This will be at least 1 year before March 2020.

Main outcome

Excess mortality in the population under investigation. Studies that will provide extractable data on the period before and during the pandemic will be included in the meta-analysis. Excess mortality will be estimated as the difference between the observed deaths within the pandemic period and the expected deaths based on historical data. The raw data on deaths will be used to estimate the pooled risk ratio with a 95% CI.

Additional outcome

Methods and data sources used in estimating excess mortality in LLMICs and factors influencing excess mortality in LLMICs.

The study selection process will be documented using the PRISMA flow diagram (see figure 1).

Data extraction

Two independent investigators will use the eligibility criteria to determine which studies need to be included in the review. Any disagreement will be resolved by discussion and a third reviewer will be consulted for a consensus to be reached.

The following data will be extracted: author(s), year of publication, the country where the study was conducted, study period, crude mortality, estimated excess mortality, estimated and registered COVID-19 mortality (if reported), mortality data sources, methods used in estimating excess mortality, identified factors or drivers of excess mortality, type of population (geographical region, cohort), population baseline characteristics and different waves of COVID-19.

Data synthesis

We will provide a narrative synthesis and meta-analysis of the findings from the included studies. Data will be presented in tabular format, focusing on estimates of excess mortality, methods used in estimating excess mortality, mortality data sources and the factors that influence excess mortality. A short comparison with methods used in developed countries will be provided. Subsequently, a structured narrative synthesis of identified limitations reported by the authors will be done.

A meta-analysis will be conducted to estimate the rate of excess mortality in LLMICs. Extracted data will be analysed using stataSE V.16 (64-bit) statistical software. The Mantel-Haenszel random-effects method will be adopted to estimate the pooled risk ratio with a 95% CI for the included studies. This random-effect model takes into account both the within-study variability (random

error) and between-study variability (heterogeneity) of the included studies. We will attempt to perform a subgroup analysis (that is, low-income countries vs lower middle-income countries, rural–urban settings, male/female comparisons and age groupings) if sufficient data are available. These will be variables as indicated in the studies that will be included.

Risk of bias (quality) assessment

Quality assessments will be performed for observational studies according to the Newcastle–Ottawa Scale (NOS) by two independent reviewers, and any disparity will be resolved by discussion or in consultation with a third reviewer. We will also provide a discussion on estimation methods and data sources.

Assessment of publication bias

To assess the publication bias of original papers to be included in the review, the funnel plot method will be used. Also, we will evaluate if all prespecified outcomes that were indicated have been reported. We will include all identified articles in our review that fulfil our eligibility criteria. To make this review transparent and reduce the likelihood of selective reporting of outcomes, the protocol was registered in PROSPERO and has been submitted for publication at *BMJ Open* to make known the search strategies and study procedures.

Sensitivity analysis

Sensitivity analyses will be carried out to investigate how study eligibility may have impacted on risk differences. This will be accomplished by running the data through a meta-analysis twice. Only studies that are known to be eligible will be included in the final meta-analysis. We will explore the robustness of the findings through inclusion/exclusion criteria and the data synthesis approaches.

Patient and public involvement

None.

ETHICS AND DISSEMINATION

As there is no primary data collection, there is no requirement for ethical review. The results will be disseminated through peer-reviewed journal publication and conference presentations.

DISCUSSION

There is still considerable uncertainty about both the direct and indirect effects of the pandemic on mortality in LLMICs. Reported estimates of COVID-19 deaths may have been under-reported or misattributed, and the pandemic's impact on mortality from other causes may have been overlooked. This review will contribute to a better understanding of the impact of the pandemic on mortality in LLMICs.

In addition, it will explore some of the highly innovative digital and statistical methods which have been developed in these countries, but which are rarely described in literature from high-income countries (HICs).[22] Most evidence on the impact of the pandemic, and the advantages and disadvantages of mitigation strategies, has come from HICs, which might lead to biases and potential blind spots about the risks, repercussions and optimal interventions specific to LLMICs.[30] This review will appraise existing estimates of excess mortality in LLMICs, assess factors determining excess mortality across different settings and socioeconomic groups, and explore innovative approaches to estimating excess mortality.

The strengths of the review will include a thorough methodology, following guidelines for systematic reviews and meta-analyses. This will minimise bias and provide a comprehensive and transparent summary of the existing evidence. A broad search strategy will be used in this review. There will be a careful assessment of the quality of included studies according to the NOS, and this will add a layer of robustness to the review's findings. A robust method of meta-analysis will be employed using appropriate statistical techniques and sensitivity analyses. This will strengthen the precision and generalisation of the findings by pooling data from the studies that will be included.

Potential methodological limitations in this review may be a scarcity of eligible primary studies meeting the criteria for inclusion. If there are too few studies, it might become challenging to draw conclusion for the various geographical regions in LLMICs. If the studies are predominantly from certain areas, the findings may not adequately account for the diversity of the excess deaths across different areas. Also, there might be large variation in methods of included studies which might pose a challenge when synthesising and comparing findings across the included studies. Despite these potential challenges, this review will help enhance the reproducibility and comparability of studies. The results will help us better understand the effect of the pandemic on mortality in different LLMICs, inform future analyses and may help identify international best practices that have contributed to lower excess mortality in particular countries.

The findings of this review will inform the methods and data sources that will be used in a planned study to estimate excess mortality in Ghana and the variables for future analyses of the determinants of excess mortality.

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Contributors JMG, WQ, JA, AJ and VB made substantial contributions to the conception and design of this systematic review and meta-analysis protocol. JMG will perform the screening, study selection and data extraction from all studies that will meet the eligibility criteria. OL will independently screen the titles and abstracts of the identified studies and WQ will adjudicate any conflicting selected studies. All authors approved the final version of this protocol.

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Competing interests None declared.

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

Patient consent for publication Not required.

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