Open access • Posted Content • DOI:10.1101/2021.09.29.21264325

Assessing the Burden of COVID-19 in Developing Countries: Systematic Review, Meta-Analysis, and Public Policy Implications — Source link

Andrew T. Levin, Andrew T. Levin, Nana Owusu-Boaitey, Sierra Pugh ...+12 more authors

Institutions: Dartmouth College, Center for Economic and Policy Research, Case Western Reserve University, Colorado State University ...+5 more institutions

Published on: 14 May 2021 - medRxiv (OSF)

Topics: Developing country, Population, Seroprevalence and Mortality rate

Assessing the Burden of COVID-19 in Developing Countries: Systematic Review, Meta-Analysis, and Public Policy Implications

Andrew Levin[1,2,3], Nana Owusu-Boaitey[4], Sierra Pugh[5], Bailey K. Fosdick[5], Anthony B. Zwi[6], Anup Malani [2,7], Satej Soman[8], Lonni Besançon[9], Ilya Kashnitsky[10], Sachin Ganesh[1], Aloysius McLaughlin[1], Gayeong Song[1], Rine Uhm[1], Gideon Meyerowitz-Katz[10,11]

1. Dartmouth College, Hanover, USA
2. National Bureau for Economic Research, Cambridge, USA
3. Centre for Economic Policy Research, London, United Kingdom
4. Case Western Reserve University School of Medicine, Cleveland, USA
5. Colorado State University, Fort Collins, USA
6. School of Social Sciences, University of New South Wales, Australia
7. Law School, University of Chicago, Chicago, USA
8. Mansueto Institute for Urban Innovation, University of Chicago, Chicago, USA
9. Faculty of Information and Technology, Monash University, Australia
10. Interdisciplinary Centre on Population, University of Southern Denmark, Denmark
11. School of Health and Society, University of Wollongong, Australia
12. Western Sydney Local Health District, Sydney, Australia

Key Points

- **Age-specific prevalence and infection fatality rate (IFR) of COVID-19 for developing countries has not been well assessed.**
- **Seroprevalence in developing countries (as measured by antibodies against SARS-CoV-2) is markedly higher than in high-income countries but still far short of herd immunity.**
- **Seroprevalence among older adults is broadly similar to that of younger age-groups.**
- **Age-specific IFRs in developing countries are roughly twice those of high-income countries.**
- **Population IFR in developing countries with satisfactory death reporting (based on UN/WHO data as of 2016) is ten times higher than in other developing countries.**
- **These results underscore the urgency of disseminating vaccines to vulnerable people in developing countries.**

Abstract

Introduction

The infection-fatality rate (IFR) of COVID-19 has been carefully measured and analyzed in high-income countries, whereas there has been no systematic analysis of age-specific seroprevalence or IFR for developing countries. Indeed, it has been suggested that the death rate in developing countries may be far lower than in high-income countries—an outcome that would be starkly different from the typical pattern for many other infectious diseases.

Methods

We systematically reviewed the literature to identify all serology studies in developing countries that were conducted using representative samples of specimens collected by early 2021. For each of the antibody assays used in these serology studies, we identified data on assay characteristics, including the extent of seroreversion over time. We analyzed the serology data using a Bayesian model that incorporates conventional sampling uncertainty as well as uncertainties about assay sensitivity and specificity. We then calculated IFRs using individual case reports or aggregated public health updates, including age-specific estimates whenever feasible.

Results

Seroprevalence in many developing country locations was markedly higher than in high-income countries but still far short of herd immunity. In most locations, seroprevalence among older adults was similar to that of younger age-groups. Age-specific IFRs were 1.3-2.5x higher than in high-income countries. The median value of population IFR was 0.5% among developing countries with satisfactory death reporting as of 2016, compared to a median of 0.05% for other developing countries.

Conclusion

The burden of COVID-19 is far higher in developing countries than in high-income countries, reflecting a combination of elevated transmission to middle-aged and older adults as well as limited access to adequate healthcare. These results underscore the critical need to accelerate the provision of vaccine doses to vulnerable populations in developing countries.

Introduction

One of the most important questions asked throughout the SARS-CoV-2 (COVID-19) pandemic has concerned the fatality rate from infection with the disease (1). Estimating fatality rates contributes to identifying the severity of the disease, the populations at risk, and to understanding the role and quality of health care services and systems (2). Two measures are commonly employed to determine mortality associated with a communicable disease: the case fatality ratio (CFR) which is the "proportion of individuals diagnosed with a disease who die from that disease and is therefore a measure of severity among detected cases"; and the infection fatality ratio (IFR) which seeks to identify the proportion of deaths among all those infected, including both detected and undetected cases (3). The ratio of fatalities to detected cases has proven problematic due to the incidence of asymptomatic or mildly symptomatic infections as well as variations in test availability and the presence of undetected infections. Consequently, the burden of COVID-19 is more accurately conveyed by assessments of IFR in a given population (1, 3, 4).

A number of recent studies have assessed the severity of COVID-19 in high-income countries with advanced healthcare systems, and several have documented a strong relationship between IFR and age; indeed, one study found that differences in the age composition of the population and the age-specific prevalence of COVID-19 accounted for nearly 90% of the variation in population IFR across locations (1). This contrasts with evidence concerning the influence of comorbidities, which while significant do not appear to have as great an impact on the COVID-19 IFR as the age of those infected (5). Currently, the literature demonstrates that while many aspects of health and the healthcare environment are related to the risk of death from COVID-19, the primary impact on IFR appears to be age (1, 6).

Previous analyses of IFR for COVID-19 have assumed that the age-stratified estimates will not vary substantially on the basis of healthcare provision and quality (4, 7). While we have substantial evidence concerning the risk of death for countries with high-income countries, based on their age and other factors, the comparison with developing nations has incorporated assumed similarities between areas (8). This is to a great extent based on the assumption held since early in the pandemic that the younger age structure of low and middle income countries, or those designated as developing countries, will lead to lower rates of morbidity and mortality due to COVID-19 (9). While the work on IFR in these locations has been impressive, it is nevertheless lacking a detailed accounting for the differences between developed and developing countries (7, 10).

Table 1: Confirmed COVID-19 Deaths as of 29 Sept 2021 (11)

Country	Cumulative Deaths	Mortality Rate per Million
USA	692,583	2,080.3
Brazil	595,446	2,782.5
India	447,751	321.3
Mexico	276,376	2,121.7
Russia	201,854	1,383.4
Peru	199,329	5,975.2
Indonesia	141,709	512.8
United Kingdom	136,746	2,004.9
Italy	130,807	2,166.9
Colombia	126,219	2,462.0

These assumptions and predictions have been challenged by more recent events and data. It is notable that in many developing nations, the deaths per capita attributable to COVID-19 is above 2,000 deaths per million population, a fatality-population ratio from the disease of >0.2%. Of the countries with the top 10 most deaths attributed to COVID-19 in the world, 7 are developing nations (see Table 1) If it were true that countries with lower median ages were likely to be spared the worst ravages of the pandemic, these enormous death tolls would not have been seen.

An important gap in knowledge is what the toll has been in developing countries, what the impact and associated implications for healthcare and vaccination priorities are, and how this is likely to impact response to the COVID-19 pandemic. If the assumption that the general morbidity and mortality rate is likely to be similar across areas is wrong, it is plausible that the death rate in less well-developed countries at similar ages would be significantly higher than the IFRs seen in high-income regions, if only because quality of public health access and information, personal protective equipment and sanitation, and health care, are all poorer.

These unknowns tie into ongoing debates about the nature of the pandemic in areas with less capacity to monitor and survey disease. Some analysts argue that the impact of COVID-19 has been modest in areas with a generally younger population (4), and that the IFR is likely to be lower in such regions for a wide range of reasons (9). On the surface, the lower death rates reported earlier by many Developing countries appeared to support this, with countries such as India seemingly having vastly lower mortality rates than evidence from elsewhere led us to expect. However, this appears to contradict very strong evidence from prior to the pandemic that demonstrates the lower quality of healthcare in regions with less ability to resource such efforts (12). Indeed, there appears to be a contradiction between the claims that developing countries have not seen a great deal of damage due to the disease and the likelihood from pre-pandemic assessments that developing countries would be at greater risk should a pandemic emerge (6).

More recently, evidence has also emerged that even these high estimates of the burden of COVID-19 in developing countries may be substantial undercounts. This has been demonstrated in a wide range of setting, for example, a study in Zambia found that only 1 in 10 of those who died with COVID-19 symptoms and a positive PCR were recorded as COVID-19 deaths in the national registry (13). This study has continued as an epidemiological investigation, and found that COVID-19 may

have caused up to 87% of all deaths in Zambia in mid-2021 (14). South Africa recorded many fewer direct COVID-19 deaths than might have been anticipated, but excess mortality in periods when the pandemic waves have surged, are highly correlated suggesting that these deaths are directly or indirectly related to the pandemic (15).The recently published World Health Statistics Report 2021 suggests that deaths from COVID-19 were closer to 3 million than the officially reported 1.8 million worldwide by the end of 2020 (16). A number of recently published studies from India suggest that COVID-19 related deaths and excess mortality were about ten times the officially reported number (17, 18).

Objectives

To shed light on these divergent viewpoints, we conducted a rigorous systematic review and meta-analysis to answer a number of core questions. We sought to utilise the best available information as of September 2021 to determine overall prevalence of COVID-19 infection in developing nations, to establish what is known about seroprevalence in relation to age within these countries, and to use such data to then establish infection fatality ratios by age for countries with relevant data available.

We then sought to relate these data to those from high-income countries and to determine whether IFR tends to be lower (as asserted by some commentators), much the same or higher in these settings. Lastly, we hoped to clarify what factors might help explain any differences observed: are these real, and if so, what are the influences upon them, or are these simply a reflection of data inaccuracies?

Methods

Our analysis assessed the burden of COVID-19 in Developing countries using the country classification system of the International Monetary Fund (8). The study was registered on the Open Science Foundation: https://osf.io/edpwv/

Review Methodology

Our meta-analysis builds on previously published work (1). To access every trial conducted in developing countries, we included both a current register of serological surveys called Serotracker (19), our own methodology published previously (1), and emails to government bodies and researchers across the world. While many places have conducted serological surveys, the number who have matching age-stratified data is much smaller and thus it was important to uncover every study that we could across the world. Where age-stratified data were not available but population-wide seroprevalence and population-wide deaths were, we computed population wide-IFRs. Full review methodology including search terms and risk of bias assessments can be found in Supplementary Appendix 1.

Inclusion Criteria:

1. Representative seroprevalence studies in developing countries, meaning: random selection of participants from a sample frame representative of the general population (such as household sampling), or sampling >50% of the general population by census (20, 21), conducted in countries classified by the IMF as Emerging and Developing Economies (EDEs).
2. Available online and accessible via translatable text if not in English

Studies that were presented in languages other than the languages spoken by study authors were translated through Google translate, and where necessary these translations were verified by a native speaker of the language (i.e. Brazilian data translated then verified with Brazilian researchers).

Exclusion Criteria:

The primary aim of this study was to examine the best-quality evidence for IFR in developing countries. At a basic level, this meant limiting our analysis to seroprevalence studies that were sufficiently robust to determine an age-stratified infection rate in the population from which to derive an age-specific IFR. As has been demonstrated in previously published work, even relatively minor divergences from population sampling can influence the seroprevalence enormously. Indeed, as demonstrated in Manaus (22), estimates of seroprevalence derived from biased blood donor samples, while useful in some ways, can provide very misleading estimates of the proportion of people who have had a past infection. This becomes even more important when considering Developing countries, as these are areas with biases that do not exist in higher-income regions and thus more care must be taken to ensure that the studies included do in fact report reliable estimates of seroprevalence in their regions.

Blood donors and studies using residual sera are two special cases that require further elucidation. These are expanded on in Supplementary Appendix 3. The full exclusion criteria for the paper can be found in Supplementary Appendix 5.

Deaths

Deaths were one of the more challenging aspects of this review. The reporting of deaths in developing countries is enormously varied, with some areas, having extremely sophisticated death reporting systems that capture deaths in multiple ways, while others have large issues and may not even have a national death reporting system at all (23, 24). China, for example, until recently did not have a complete national death collection register (25). While previous examinations of IFRs in developing countries have largely ignored this issue, we considered this a serious problem that must be addressed if more accurate estimates are to be generated. We dedicated a significant effort to examining the death data from each country, with the full methodology in Supplementary Appendix 2. IFRs were calculated as the simple ratio of deaths to infections for a given area and age-bracket.

Covariates

We selected covariates that were judged likely to have an impact either on the IFR of COVID-19 itself or on the accuracy of official data on COVID-related mortality based on prior research and expertise. Where possible, we extracted these covariates at a state or regional level within a country, otherwise they were identified at national level. A full list of covariates and the method of extraction can be found in Supplementary Appendix 4.

Serology Only

To address the interest in disease prevalence in developing countries, we included locations for which there was insufficient death data to provide an IFR estimate and estimated the number of infected individuals. Without estimating the IFR, we addressed the question of how many people were likely to have been infected in these areas, once adjusted for test sensitivity and specificity.

Out-of-Sample Estimates

Geographically overlapping samples are an issue for meta-analyses such as ours, as they can bias the results with more than one sample from the same population. To avoid this issue, where there was

more than one estimate for the same location we included only one estimate in the main analysis and categorized the other estimate(s) as out-of-sample. Locations with 0 reported COVID-19 deaths were also categorized as out-of-sample, as were locations with less than 15,000 people.

Statistical Analysis

We use a Bayesian modelling framework to simultaneously estimate age-specific prevalence and infection fatality rates (IFRs) for each location in our study. We model age-specific prevalence for each location at the resolution of the serology data reported. We model the number of people that test positive in a given study location and age group as coming from a binomial distribution with a test positivity probability that is a function of the true prevalence, sensitivity and specificity, accounting for seroconversion and seroreversion (see Supplementary Appendix 6). As in Carpenter and Gelman (2020) (26), acknowledging the uncertainty in the test assay sensitivity and specificity itself, we consider sensitivity and specificity to be unknown and directly model the lab validation data (e.g., true positives, true negatives, false positives, false negatives) for each test. Independent weakly informative priors are placed on the seroprevalence parameters, and independent, informative priors akin to those in Carpenter and Gelman (2020) (26) are placed on the sensitivity and specificity parameters.

Prevalence for a given age group and location is estimated by the posterior mean and equal-tailed 95% credible interval. Uniform prevalence across age is deemed plausible for locations where the 95% credible intervals for the ratio of seroprevalence for age 60 and older over the seroprevalence estimate for ages 20 to 60 contains 1.

In order to avoid assumptions about the variability of prevalence across age within a serology age bin, we aggregate deaths for each location to match their respective serology age bins. We model the number of individuals at a given location and age group that are reported dying of COVID-19 as Poisson distributed with rate equal to the product of the age group IFR, age group population, and age group prevalence. Independent mildly informative priors are assumed on the age group specific IFR parameters. This model provides age-group level IFR estimates for locations where deaths were reported separately for different age bins and an overall IFR estimate for locations with only total death data.

We compared our IFR results to prior results for high-income areas (2). Where possible, we divided locations into the most granular possible estimate by the availability of death data, to obtain more granular figures, such that national studies with individual state data were analysed by state if death data was available.

The model was implemented in the programming language R, with posterior sampling computation implemented with the `Stan` software package (27).

Results

We identified a total of 2,347 study records, with 2,281 records identified from online databases and a further 66 from Twitter and Google Scholar. After excluding 2,061 records we assessed 286 records for inclusion in the final analyses. There were a total of 88 studies that could be used to describe either seroprevalence or IFR. The final sample for IFR estimates included 56 estimates from 21 developing countries. The search and exclusion process can be seen in Supplementary Appendix 11. The distribution of included seroprevalence estimates can be seen in Figure 1.

Figure 1 - Map of Study Locations

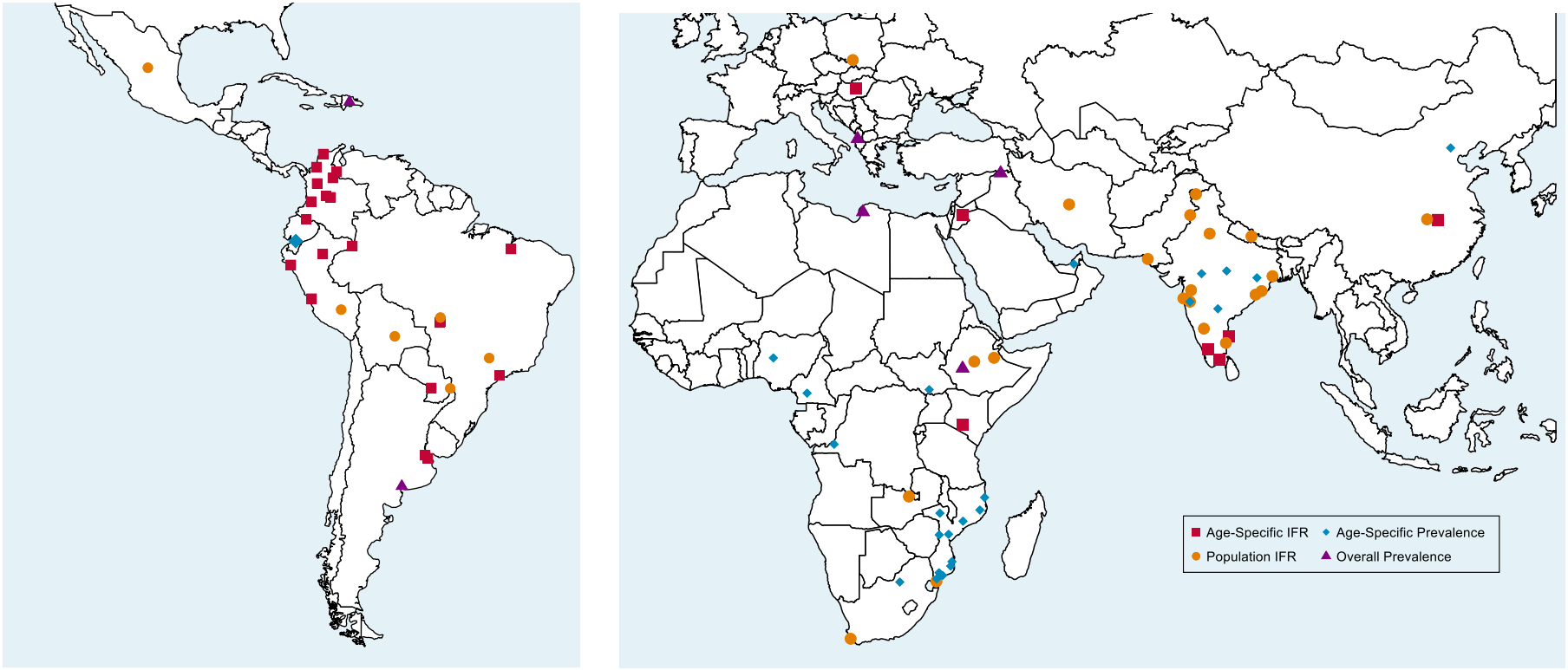

Figure 1 – Map of study locations with specifics of how these locations were used in the study. St. Petersburg, Russia (not shown on the map) has total IFR data.

Figure 2 - Seroprevalence during the First Wave of the COVID-19 Pandemic

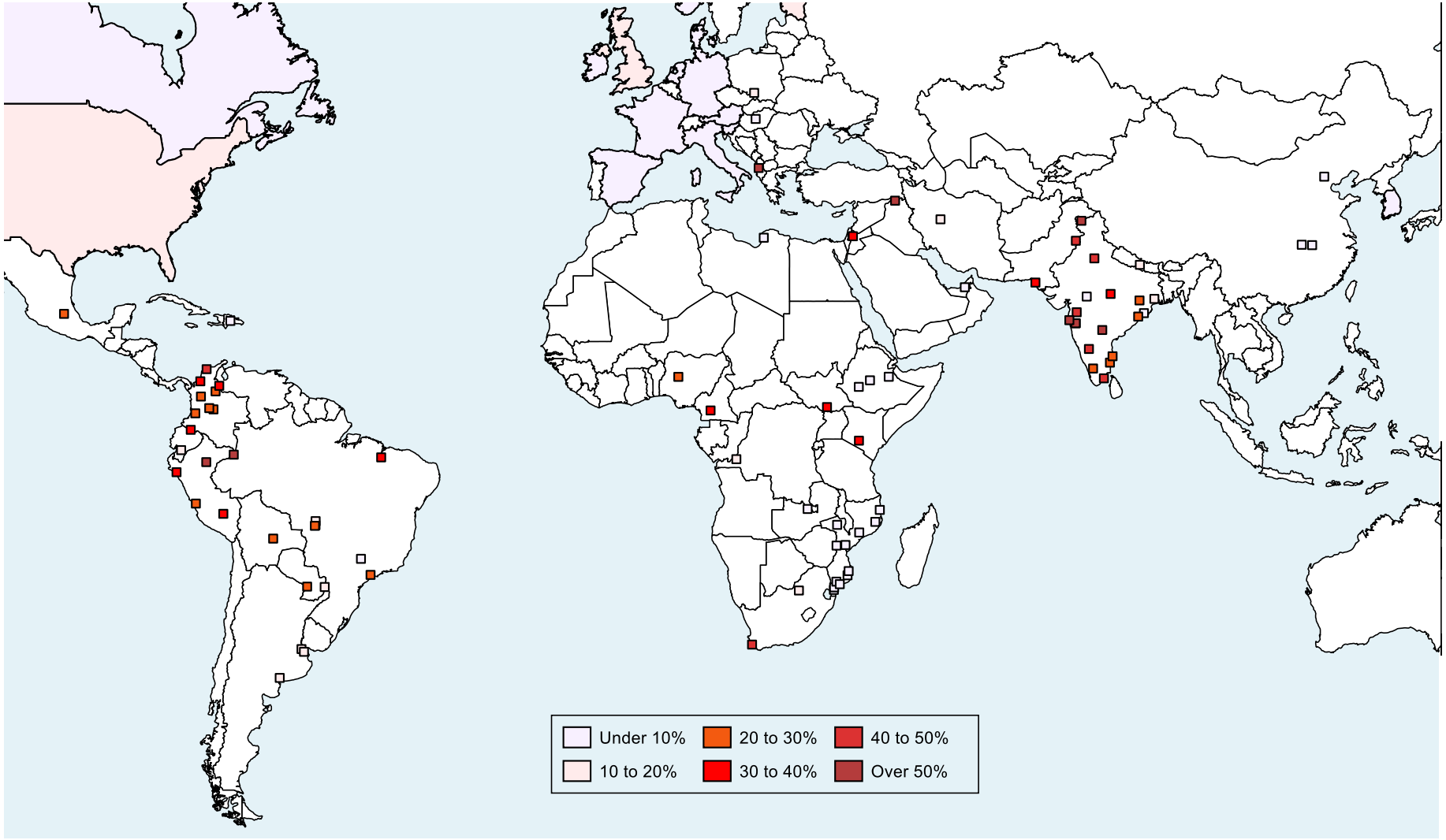

Figure 2 – Map of areas with seroprevalence after the first wave. St. Petersburg, Russia (not shown on the map) had measured seroprevalence of 11% as of June 2020. This represents the same seroprevalence as used in IFR calculations.

Seroprevalence

In contrast to high-income countries, the seroprevalence across developing countries was substantially higher after a single wave. This is shown in the map on Figure 2, where the majority of high-income locations have seroprevalence below 20%, while a large number of developing countries have seroprevalence far exceeding this rate.

A major finding of this research was that seroprevalence in the majority of developing areas was consistent across age strata. What this means is that infection rates in older age groups were similar to those in younger age groups, which is in contrast to observed rates of infection seen in high-income countries (1). This is displayed below in Figures 3 and 4. Figure 3 shows the heatmap of age-specific seroprevalence in included locations, demonstrating that for the majority of developing countries the proportion of people with evidence of past infection is consistent across age strata. Figure 4 demonstrates this numerically, showing that the majority of developing countries have seroprevalence consistent with no protection of older age groups (i.e. equal infection rates between older and younger adults).

Figure 3 - Age-Specific Seroprevalence by Location

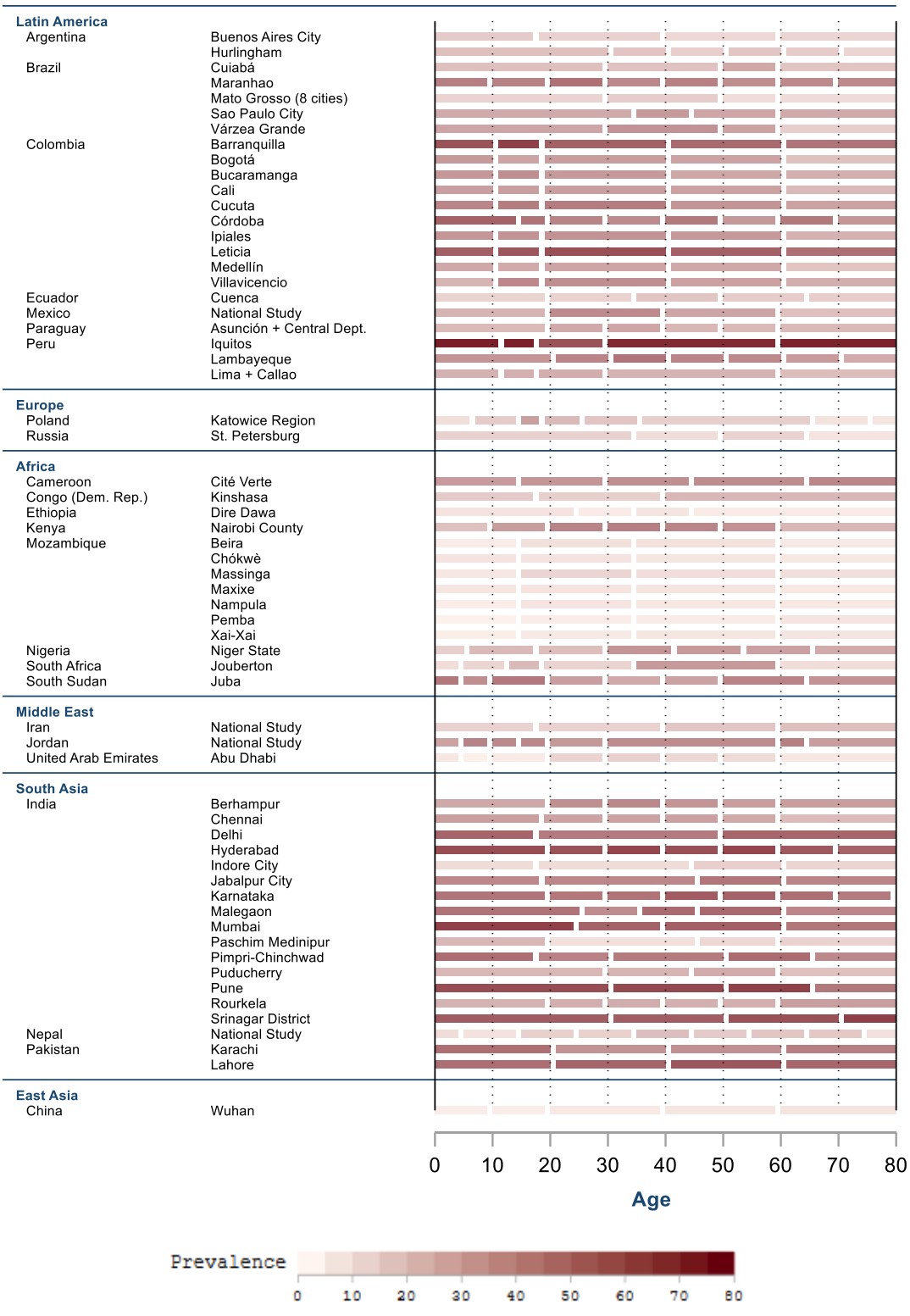

Figure 3 – Map of areas with seroprevalence after the first wave

Figure 4 - Ratio of Seroprevalence for Older Adults (60+ years) Compared to Younger Adults (18-59 years)

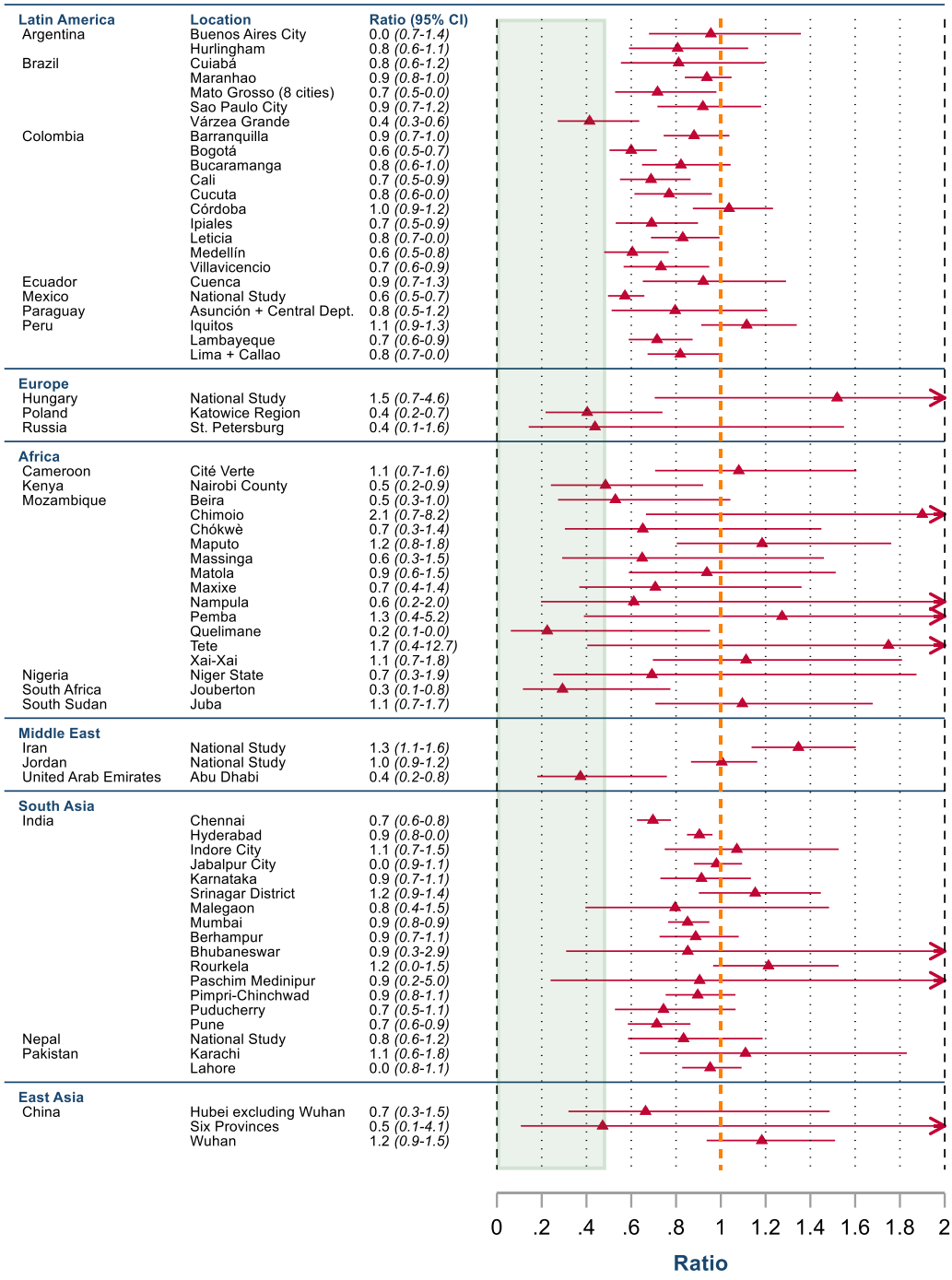

Figure 4 - Green shaded area – range of AEs for ratio after first wave (1), orange line – ratio of 1. This figure demonstrates that most developing countries are above or consistent with 1, and there was very little protection of the elderly population across locations in developing countries identified.

Population IFRs

The primary output of our model is the population IFR. This is an estimate of the *total* number of deaths over the *total* number of infections for a given location between the ages of 18-65. These estimates are presented in figure 5 for each location. Here the age-specific IFR estimates for each location were weighted based on the location specific prevalence of each age group and a common baseline population structure so that these population IFR estimates are comparable across locations with differing population structure (see Supplementary Appendix 12).

Figure 5 - Population IFR for Ages 18 to 65 Years

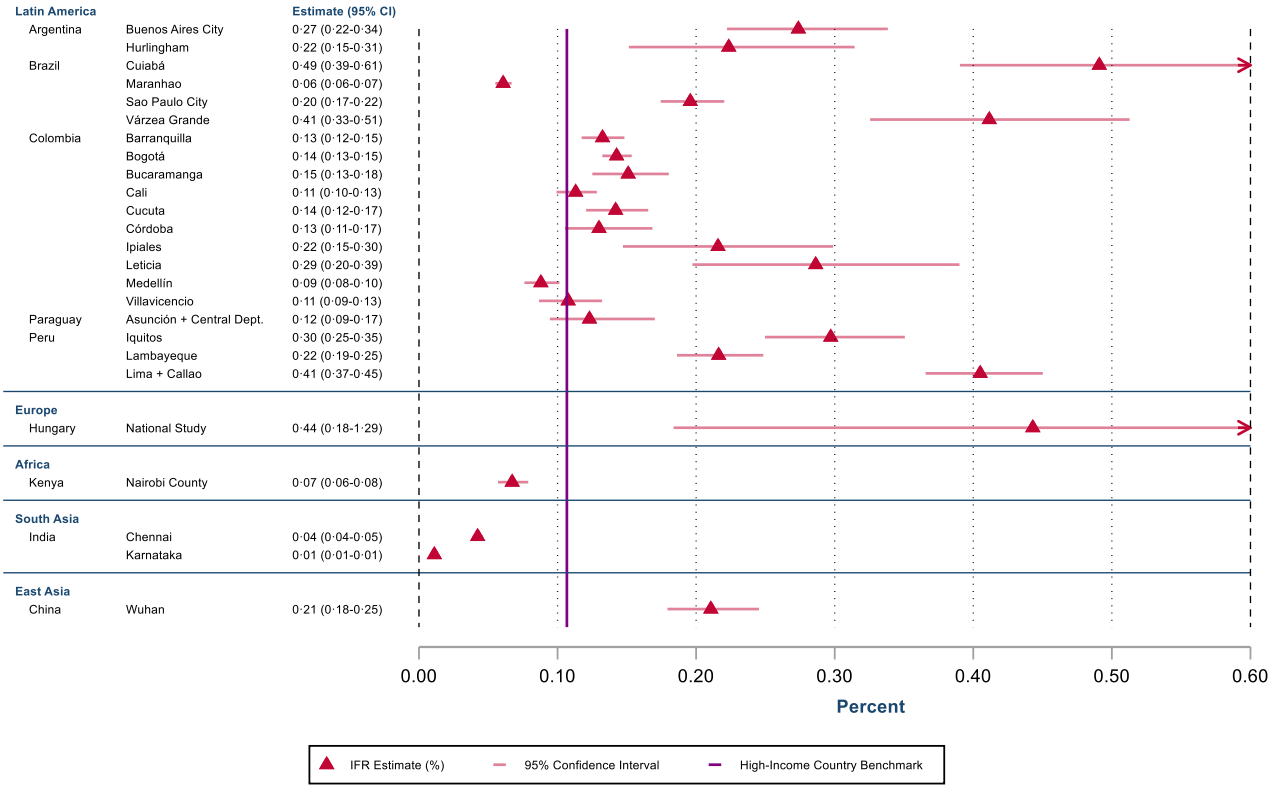

Figure 5 – IFR estimates for the population aged 18-65 across locations.

Figure 6 - Metaregression Results for Locations with Well-Certified Deaths > 50%

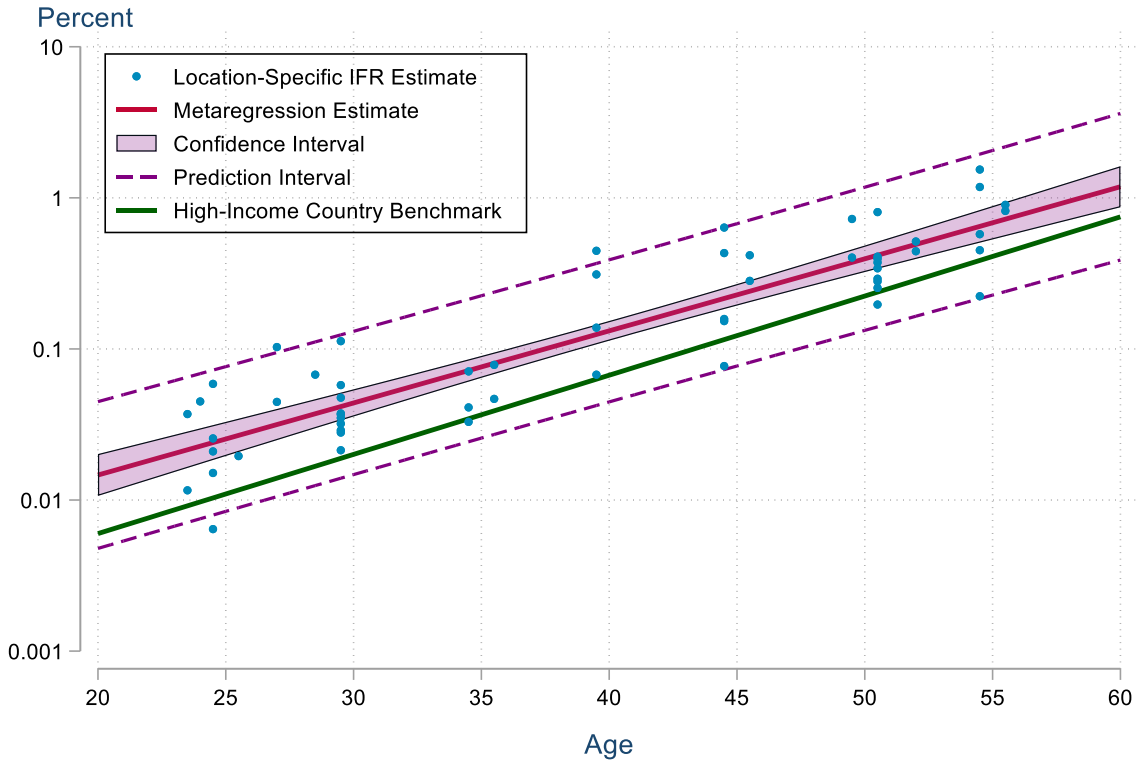

Figure 6 – IFR estimates for the population aged 18-65 across locations.

There was a great deal of heterogeneity in these population IFRs. There were 5 locations for which the population IFR for ages 18-65 was lower than earlier AE estimates, 4 locations for which the results were consistent with earlier AE estimates, and 16 locations for which the results were higher. Most estimates above the predictions for high-income countries were substantially higher, with 8 locations having a population IFR for ages 18-65 more than double that of the high-income prediction. There was also disparity between locations with very similar population characteristics, for example the enormous variation seen in different estimates from areas within Colombia.

To examine the curve of age-specific fatalities in developing countries compared to high-income countries, we re-created a metaregression of IFR on age in previously published work (1). The full methodology for this is given in Supplementary Appendix 7. The comparison can be seen in Figure 6. At 25 years of age, the mean IFR in developing countries is 2.3times higher than that in high-income countries. At older ages, this discrepancy is reduced, with only a modestly increased risk at age 80. These comparisons are shown in Table 2 below.

Table 2 – comparisons of the ratio of IFR between low and high-income areas by age.

Age	IFR (95% CI)	High-Income Benchmark	Ratio
10	0.005 (0.003-0.008)	0.002	2.5
15	0.008 (0.006-0.012)	0.003	2.7
20	0.015 (0.011-0.020)	0.006	2.5
25	0.025 (0.020-0.033)	0.011	2.3
30	0.044 (0.036-0.054)	0.020	2.2
35	0.076 (0.064-0.090)	0.037	2.1
40	0.13 (0.11-0.15)	0.067	1.9
45	0.23 (0.19-0.27)	0.12	1.9
50	0.40 (0.32-0.48)	0.22	1.8
55	0.68 (0.53-0.88)	0.41	1.7
60	1.18 (0.87-1.62)	0.75	1.6
65	2.05 (1.41-2.99)	1.37	1.5
70	3.55 (2.29-5.52)	2.50	1.4
75	6.15 (3.71-10.20)	4.57	1.3
80	10.65 (6.01-18.89)	8.36	1.3

IFR estimates varied fundamentally differently for higher and lower age groups. At lower age groups, the number of deaths becomes very small, and thus the uncertainty is very large regarding the IFR. Conversely, at older ages the number of infections and deaths can be very small in countries with extremely small populations of those aged over 65, and thus these estimates are also uncertain. The full figures across all ages can be found in Supplementary Appendix 8.

There remains considerable heterogeneity across developing nation IFRs. Hungary, which is at the higher end of emerging economies, was not enormously above the anticipated IFR for an AE. However, most countries in south and Central America had death rates 2 or 3 times higher than those in high-income areas, with Peru in particular having a very high death rate per infection.

India appears to be an outlier in this analysis in a number of ways. Most locations in India had a lower than predicted IFR, with some areas being up to 10x lower than other estimates from within the same state of the country. It is noteworthy that areas in India are not consistent with each other, with higher-income regions often having higher inferred IFRs than lower-income areas.

Figure 7 - Population IFR and Well-Certified Death Registrations

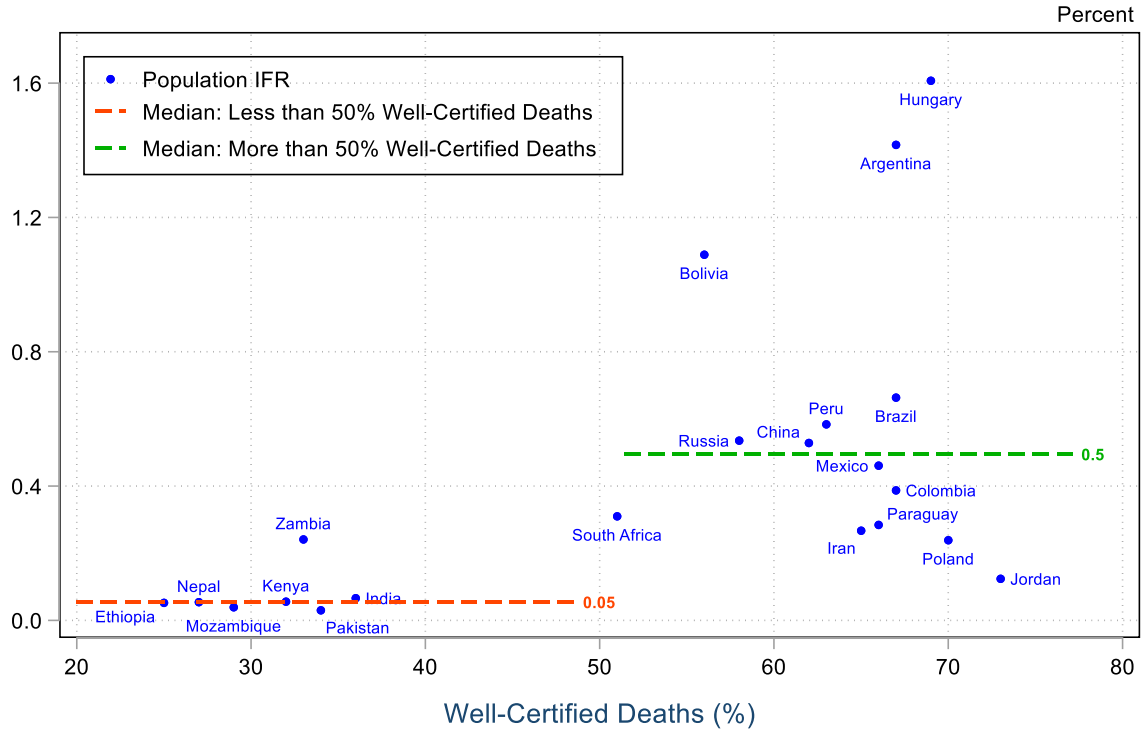

Figure 7 – Population IFR for regions divided into areas with <50% well-certified deaths and areas with >50% well-certified deaths as per SDGs.

Covariates

A full examination of covariates considered in this analysis is presented in Supplementary Appendix 9. Using the Sustainable Development Goals (SDGs) definition from 2016 of deaths properly recorded (24), we found that the median population IFR in areas where <50% of deaths were well-certified was 0.05% compared to a mean population IFR of 0.5% in areas where >50% of deaths were well-certified. There was a strong correlation between death reporting adequacy prior to the pandemic and the IFR.

Discussion

Our analyses build on the work showing that age has a strong impact on COVID-19 risk, and demonstrate that the region of the world also plays an important role in the likelihood that someone will die if they catch the disease. Compared to a person of similar age and other demographics such as gender, ethnicity, who was born in a country such as the United States, a person born in a country such as Gabon has a large increased risk of death, although this difference appears to be smaller for very old people. This overturns the assumption that COVID-19 infections are primarily a problem for high-income countries with ageing populations, as it shows that the risk of severe illness and death is substantially increased in those settings with fewer resources and weaker health systems to manage

infections. In particular, while the risk of death appears to converge at higher ages, most adults in developing countries appear to be at a very large increased risk of death from COVID-19 when compared to adults in high-income countries.

Implications for developing countries

The implications for estimating the magnitude of COVID-19 fatalities in developing countries are considerable. It has previously been demonstrated that these figures may be substantial underestimates (13), and our study confirms that the most likely explanation for places with very low death rates is simply that these places are not recording COVID-19 deaths adequately.

In particular, this is related to the proportion of deaths that are assigned to so-called "garbage codes" (24). These deaths are, by definition, not included in national tallies of the population that has died from COVID-19. In places where death reporting systems are adequate to record deaths, the IFR is on average 10x higher than in places where many deaths are left uncertified. Moreover, those places where deaths are not age-stratified, or where there is not granular enough data to derive age-specific estimates, are also the developing countries with by far the lowest death rates. We can say with some certainty that the true difference between developing countries with many similar characteristics, such as areas of Brazil and India, is probably minimal, and that the apparent difference in COVID-19 death rates is due to incomplete death reporting systems.

Our model makes a very strong case for swifter action on vaccine equity. While countries have largely sought to protect their own populations, there is increasing commitment to ensuring that key populations in low and middle income countries receive vaccines, at a minimum for their front-line health and other personnel. It is widely accepted that failing to control the pandemic across the globe will contribute to the emergence of additional strains of COVID-19, potentially undermining the efficacy of available vaccines and stimulating the requirement for repeated vaccine updates and modifications (28). Current vaccine distribution efforts are grossly inequitable (29). This also ties into another important finding, which is that the predominant explanation for very low death rates appears to be underreporting of deaths. This provides an urgent impetus for higher-income nations to assist with the development and implementation of better reporting systems for lower-income areas of the world.

Our research has demonstrated how damaging COVID-19 can be in areas where healthcare resources are strained. While it has been to argued that developing countries are likely to have been spared the travails of pandemic disease due to their younger population, our estimates show that this is not precisely true. While younger people are much less likely to die from an infection, in places with very low resources there are large numbers of deaths that may have been prevented with better access to medical services. Focusing only on survival rates also obscures the large number of deaths that occur when many people are infected (30), SARS-CoV-2's relatively high fatality rate in comparison to other pathogens and other causes of death(31), and non-mortality harms of COVID-19, such hospitalization from serious disease (32).

Another important facet of our results is that seroprevalence was both higher and consistent across age-groups in developing countries, in contrast to the lower rates of infection seen in high-income areas, particularly in older populations. This demonstrates that, despite efforts, it has not been possible to protect elderly populations in these lower-income settings, which has likely contributed to the terrible toll that COVID-19 has had in these areas. Despite the much higher disease rates in developing countries, they were still far off proposed herd immunity thresholds, underscoring the urgent need for vaccines in these places.

We have also worked through several potential explanations that have been posited for why some developing countries have seemed less impacted by the pandemic. In general, the most likely explanation for large differences in reported IFR appears to simply be the recording of deaths in each region. While other factors such as GDP are correlated with death rates, they are also highly correlated with death reporting, and a likely explanation appears to be that the majority of places with very low IFRs are simply those places that cannot capture COVID-19 deaths adequately. This does not exclude some impact from other covariates, but it is likely that this impact is small.

Limitations

As with all research, our study is subject to a number of limitations. Firstly, while we made every effort to capture seroprevalence data, including corresponding with dozens of researchers and public health officials worldwide, it is likely that some studies have been missed. In a global pandemic, there is simply so much activity occurring that even the most complete searches are often outdated weeks after they are done – within the timeframe of academic publication, it is almost certain that further records have emerged which would have matched our inclusion criteria. Nevertheless, we believe that this study represents the most complete current accounting of seroprevalence estimates that meet our inclusion criteria and thus are sufficiently robust as to estimate age-stratified IFRs in developing countries.

The uncertainty around data is a major issue that is unavoidable in this research. Developing countries rarely have the detailed, structured data systems that higher income nations have, and thus extracting data becomes a more challenging prospect. In many cases for covariates rather than using data from the countries themselves we relied on international bodies who collate and process this information – while these are the best sources of data available that does not necessarily mean they are perfect.

As with all studies of this type, the ecological fallacy is an inherent limitation. Using country or region levels for covariates means that the diversity which is apparent even in subnational units is homogenized, and important granularity may have been lost. For example, the difference between slums and non-slum areas in Mumbai is likely to be very large in terms of life expectancy, but there are no current figures allowing us to adjust for this discrepancy and therefore Mumbai is represented by a single estimate of life expectancy in the model. Moreover, covariate data on this scale is reliant on reporting systems that themselves are not regularly updated, meaning the information used in the study may have been old.

Full data on COVID-19 seroprevalence and deaths was not available for every area studied. While we attempted to correct for this in the analysis, it is nevertheless a limitation to the research.

Conclusion

This systematic review and meta-synthesis demonstrates that the risks of COVID-19 are not confined to higher-income regions. In fact, developing countries with lower resources are likely to have suffered more during the pandemic than previously recognized, with substantially higher death tolls and a greater burden of disease than official numbers show. This is likely in part because low-income areas are less able to protect vulnerable populations, as well as lower access to health services in these countries. It is likely that the true burden of COVID-19 is far larger than the current estimates, based on flawed reporting systems, suggest. This makes a strong case for the rapid redistribution of vaccines globally, and should herald an end to the spurious arguments that developing nations have not been severely impacted by COVID-19 during the pandemic.

Statements of Competing Interests

This work was not funded and the authors report no financial or other conflicts of interest.

Code and Data

All data is available publicly online, code is available on request.

References

1. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. European Journal of Epidemiology. 2020;35(12):1123-38.
2. Estimating mortality from COVID-19. 2020.
3. Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection-fatality rates. medRxiv. 2020:2020.05.03.20089854.
4. Ioannidis JPA. Infection fatality rate of COVID-19 inferred from seroprevalence data. Bulletin of the World Health Organization. 2021;99(1):19-33f.
5. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.
6. Chen X, Chen Z, Azman AS, Deng X, Sun R, Zhao Z, et al. Serological evidence of human infection with SARS-CoV-2: a systematic review and meta-analysis. The Lancet Global Health.
7. O'Driscoll M, Ribeiro Dos Santos G, Wang L, Cummings DAT, Azman AS, Paireau J, et al. Age-specific mortality and immunity patterns of SARS-CoV-2. Nature. 2021;590(7844):140-5.
8. World Economic and Financial Surveys World Economic Outlook Database—WEO Groups and Aggregates Information. 2021.
9. Ioannidis JPA. Reconciling estimates of global spread and infection fatality rates of COVID-19: An overview of systematic evaluations. European Journal of Clinical Investigation. 2021;51(5):e13554.
10. Brazeau N, Verity R, Jenks S, Fu H, Whittaker C, Winskill P, et al. Report 34: COVID-19 infection fatality ratio: estimates from seroprevalence. Imperial College London; 2020.
11. COVID-19 Data Explorer: Our World In Data; 2021 [Available from: https://ourworldindata.org/explorers/coronavirus-data-explorer.
12. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. The Lancet. 2006;368(9534):505-10.
13. Mwananyanda L, Gill CJ, MacLeod W, Kwenda G, Pieciak R, Mupila Z, et al. Covid-19 deaths in Africa: prospective systematic postmortem surveillance study. BMJ. 2021;372:n334.
14. Gill CJ. Latest data from Lusaka morgue analysis shows spike in COVID-19 deaths. The Conversation. 2021.
15. Report on Weekly Deaths in South Africa 2021 [Available from: https://www.samrc.ac.za/reports/report-weekly-deaths-south-africa.
16. The true death toll of COVID-19. World Health Organization; 2021.
17. Ramachandran S, Malani A. All-cause mortality during SARS-CoV-2 Pandemic in India: Nationally-representative estimates independent of official death registry. medRxiv. 2021:2021.07.20.21260577.
18. Deshmukh Y, Suraweera W, Tumbe C, Bhowmick A, Sharma S, Novosad P, et al. Excess mortality in India from June 2020 to June 2021 during the COVID pandemic: death registration, health facility deaths, and survey data. medRxiv. 2021:2021.07.20.21260872.
19. Bobrovitz N, Arora RK, Yan T, Rahim H, Duarte N, Boucher E, et al. Lessons from a rapid systematic review of early SARS-CoV-2 serosurveys. medRxiv. 2020:2020.05.10.20097451.

20. Community Assessment for Public Health Emergency Response Toolkit. CDC; 2019.
21. Population-based age-stratified seroepidemiological investigation protocol for COVID-19 virus infection. World Health Organization; 2020.
22. Buss LF, Prete CA, Abrahim CMM, Mendrone A, Salomon T, de Almeida-Neto C, et al. Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic. Science. 2021;371(6526):288-92.
23. Karlinsky A, Kobak D. Tracking excess mortality across countries during the COVID-19 pandemic with the World Mortality Dataset. eLife. 2021;10:e69336.
24. Fullman N, Barber RM, Abajobir AA, Abate KH, Abbafati C, Abbas KM, et al. Measuring progress and projecting attainment on the basis of past trends of the health-related Sustainable Development Goals in 188 countries: an analysis from the Global Burden of Disease Study 2016. The Lancet. 2017;390(10100):1423-59.
25. Zeng X, Adair T, Wang L, Yin P, Qi J, Liu Y, et al. Measuring the completeness of death registration in 2844 Chinese counties in 2018. BMC Medicine. 2020;18(1):176.
26. Gelman A, Carpenter B. Bayesian analysis of tests with unknown specificity and sensitivity. medRxiv. 2020:2020.05.22.20108944.
27. Team SD. RStan: the R interface to Stan. R package version 2.19.3. 2020.
28. COVAX: With a fast-moving pandemic, no one is safe, unless everyone is safe: World Health Organization; 2020 [Available from: https://www.who.int/initiatives/act-accelerator/covax.
29. Keith Collins JH. See How Rich Countries Got to the Front of the Vaccine Line. New York Times. 2021.
30. Moser W, Fahal MAH, Abualas E, Bedri S, Elsir MT, Mohamed MFERO, et al. Retrospective mortality and prevalence of SARS-CoV-2 antibodies in greater Omdurman, Sudan: a population–based cross–sectional survey. medRxiv. 2021:2021.08.22.21262294.
31. Lapidus N, Paireau J, Levy-Bruhl D, de Lamballerie X, Severi G, Touvier M, et al. Do not neglect SARS-CoV-2 hospitalization and fatality risks in the middle-aged adult population. Infectious Diseases Now. 2021;51(4):380-2.
32. Herrera-Esposito D, de los Campos G. Age-specific rate of severe and critical SARS-CoV-2 infections estimated with multi-country seroprevalence studies. medRxiv. 2021:2021.07.29.21261282.