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

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a. Systematic Review Methodology

Search Procedure

We searched Serotracker using *"household and community samples"* and *"persons living in slums"* in the *"demographics"* field. We also searched MedRxiv, PubMed, Google Scholar, Biorxiv, SSRN, Twitter, and the Pan American Health Organization database using the pre-specified search term *"COVID-19 seroprevalence".* Then we cross-checked with recently published systematic reviews of worldwide seroprevalence (1-4), while identifying further studies by searching the grey literature and government websites where appropriate. This included searching using the term *"COVID-19 seroprevalence"* on Google in languages on Google Translate such as Portuguese, Spanish, English, French, German, and Italian, with an additional search for *"inquérito sorológico, COVID-19".* Duplicates were reviewed by authors on Google sheets and resolved independently.

We completed searches on October 22nd, 2020, and at least monthly afterwards until July 14, 2021. We also performed searches monthly until September 22, 2021 during initial drafting of our paper. After our completing initial draft, we performed additional searches monthly up to December 17, 2021, which represented the final cut-off date for studies included in our analysis. Only studies with results from an official source were included, such as a published paper, pre-print, presentation by government officials, or the website of the institution that performed the study. If a press report or another unofficial source was found, we performed more detailed searches using information from the unofficial source to find a matching official source. Study authors were contacted by email or Twitter for further information, when needed. We also ran detailed searches after September 22, 2021 on older studies for which preliminary results were found by September 22, but for which updates were posted after September 22. We include links to the studies at each location in the appendix folder of our GitHub repository.

Searches were conducted by one member of the team and then repeated to ensure consistency by another. Data were similarly extracted by one member then cross-checked by another. No data collection was automated. This process was recorded by the team working across regions in Google sheets. Data collection is more fully described below but included extracting seroprevalence information from included studies by age where available, as well as death data specific to COVID-19 from each country/region with valid seroprevalence information. Where serology data was not evident in publicly available reports, we reached out to researchers and public health officials using both email and social media. For death data we largely relied on publicly available official reports.

Studies were reviewed by two authors and screened for inclusion. Disagreements were resolved through discussion between all authors at weekly meetings and via email. Where essential data were missing despite efforts to access them, we excluded the study from our synthesis, as noted in supplementary appendix section 1.b. Our aim was to provide the most robust estimate of age-specific IFR in developing countries, and thus we considered it inappropriate to rely on potentially flawed assumptions regarding these studies in our analysis.

Exclusion of Convenience Samples

Blood donor studies are widely used as blood donors are a convenient population from which to draw a population estimate – donors already have blood taken, can be tested easily, and tend to include people from a relatively wide area (5). However, as has been noted in research prior to the pandemic, donors are a highly selected sample and donor studies often have a large bias in terms of estimates of seroprevalence for other diseases (6, 7). Moreover, in many areas, particularly at initial stages of the pandemic, donating blood was one of few methods available to access a serological test. It is unclear which direction this bias generally runs, especially considering the dynamics of a novel pathogen in the community (8).

Residual sera studies examine clinical blood samples taken initially for other reasons. These samples have an obvious bias in that they are representative of people going to have blood taken for reasons other than SARS-CoV-2 tests, a group that may not be representative of the general population (9). Bayesian procedures can be used to incorporate studies of convenience samples (such as residual sera from blood donors or commercial lab tests) in producing estimates of population infection rates by accounting for uncertainty about the magnitude and direction of bias (10); however, we excluded such studies from our analysis to avoid introducing these additional sources of bias. Convenience sampling of such populations may be sufficient for other purposes, but probabilistic selection from a representative sample frame better facilitates accurate estimation of population-wide infection rates (3, 11).

Risk of Bias

In assessing the risk of bias for each location, we considered three specific factors: (1) the serology study's rate of non-response; (2) the risk of bias due to seroreversion if the study used an assay with high risk of seroreversion but information was not sufficient for adjusting sensitivity accordingly; and (3) the risk of death undercounting was elevated due to low proportion of well-certified deaths. These risk of bias assessments are provided in the appendix folder of our GitHub repository.

Publication Bias

In this context, publication bias in which studies exhibiting certain findings are more likely (or not) to be published, is very unlikely to have an impact, as studies with both high and low seroprevalence estimates are of interest to the scientific literature. Consistent with this, in prior work we found no evidence of publication bias for seroprevalence studies from high-income countries (12). However, to mitigate the risk of publication bias influencing our results, we included lengthy searches of grey literature, following up on media reports of seroprevalence studies to ensure that every age-stratified that we were able to identify was in our metasynthesis.

b. Full Inclusion / Exclusion Criteria

We included only studies that met both of the following conditions:

1. Report seroprevalence from a representative sample 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 (13-15), conducted in countries classified by the International Monetary Fund as "Emerging and Developing Economies" (16).
2. Available online and accessible in English, or via translatable text if not in English.

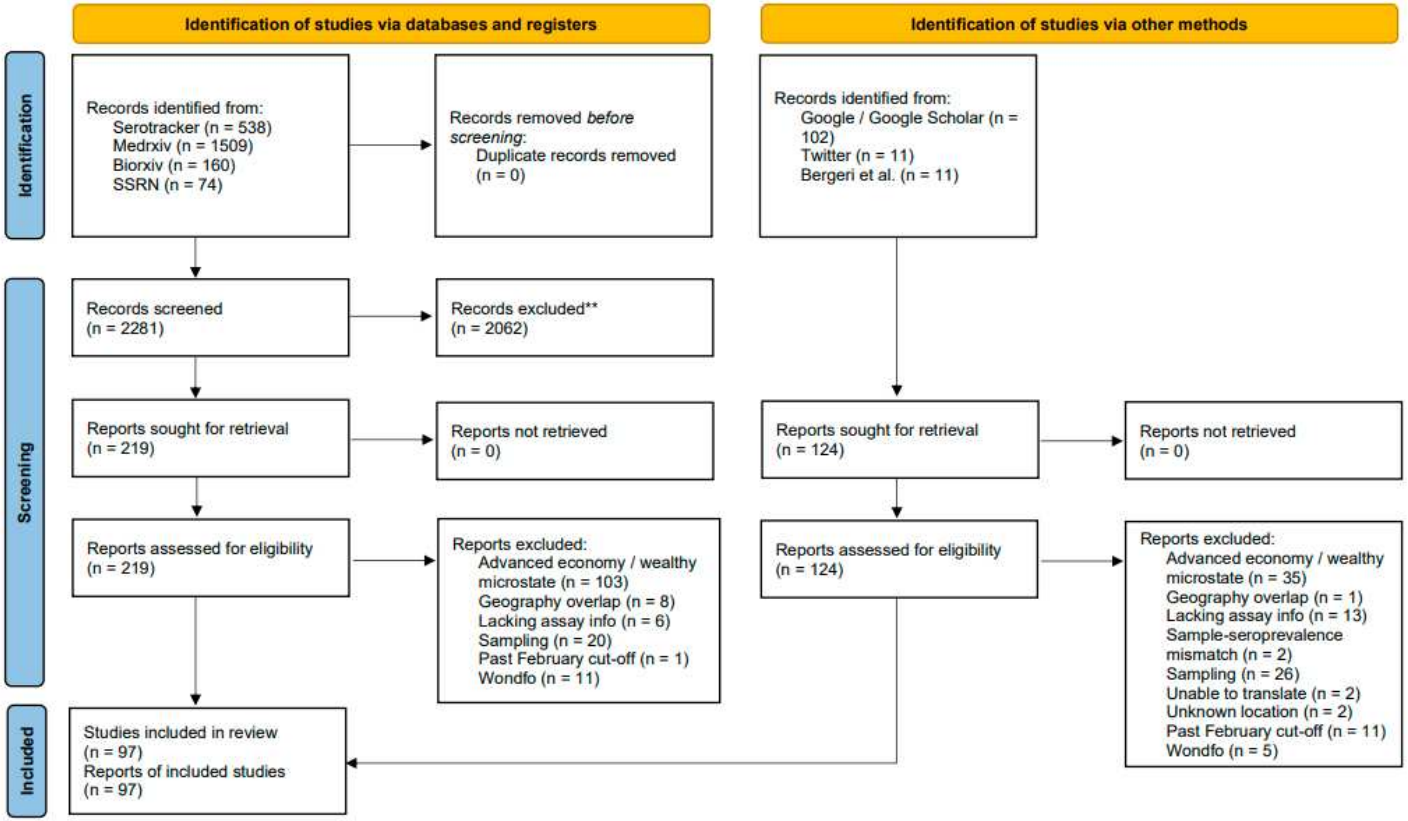
For studies with no reported age-stratified seroprevalence, but sufficient information to otherwise calculate age-stratified IFRs, we calculated these IFRs assuming equal seroprevalence across age-groups instead of excluding the study. When total sample size and age-specific seroprevalence were known, but age-specific sample sizes were not precisely reported, age-specific sample size was imputed based on the age-distribution of the general population. We excluded:

1. Convenience samples (3), including those utilizing residual sera from clinical specimens and blood donors (see the "*Blood Donors and Residual Sera*" section below), dialysis centres, healthcare workers, and actively recruited participants constituting less than 50% of the total population sampled (3, 12, 17).
2. Studies sampling a high-income country, as classified by the International Monetary Fund (16), or a wealthy micronation such as Andorra or Monaco.
3. Studies in which sampling extended after February 2021, to help mitigate the risk of seroreversion on longer timeframes (see supplementary appendix section 2.a).
4. If gender ratios were reported and less than 35% of the sample reported as male or female, in the absence of cited evidence that the study's gender ratio matched the general population.
5. Studies that used the Wondfo serology assay, for the reasons discussed in section 2.b below.
6. Studies that did not report the total number of individuals tested or seroprevalence.
7. Studies using serology assays with insufficient data for estimating sensitivity and specificity from a known number of tested samples.
8. IFR estimate excluded if: A) the sampling start-week or end-week was not known to allow for accurate determination of the corresponding number of COVID-19 deaths, B) test-adjusted population-wide seroprevalence overlapped with 0%, or C) samples were taken during an accelerating outbreak in which reported COVID-19 deaths increased by a factor of three or more from the midpoint date of sampling to 4 weeks later (12).
9. Seroprevalence estimate excluded if both of the following conditions were met: A) IFR estimate was excluded for other reasons listed above, and B) the study overlapped geographically with another included study. This geographical exclusion avoided oversampling the same location (12). IFR estimates that met condition B but not condition A are discussed in the out-of-sample analysis below.

Our "out-of-sample" analysis included studies that met at least one of the following conditions:

1. IFR estimate for a location that geographically overlapped with an included study, and thus inclusion of both estimates risked oversampling the same location. IFR estimates for those locations are provided in supplementary appendix section 3.i.
2. Zero COVID-19 deaths reported for the sampled location, making the calculated IFR non-robust (18). Consequently, our GitHub repository includes seroprevalence estimates for these out-of-sample locations, but IFR estimates were not computed.
3. The total population from which the sample was drawn was less than 30,000, which may not reflect the wider population of the region. Consequently, our GitHub repository includes seroprevalence estimates for these out-of-sample locations, but IFR estimates were not computed.
4. Seroprevalence data from five cities in Pakistan did not become available until after our final cutoff.

c. PRISMA Flow Diagram



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

d. Death Data

Building on our prior work (12), we assess the length of the lag between the midpoint of serology sampling and the time at which COVID-19 deaths were reported. The time interval between symptom onset and death had an interquartile range (IQR) of:

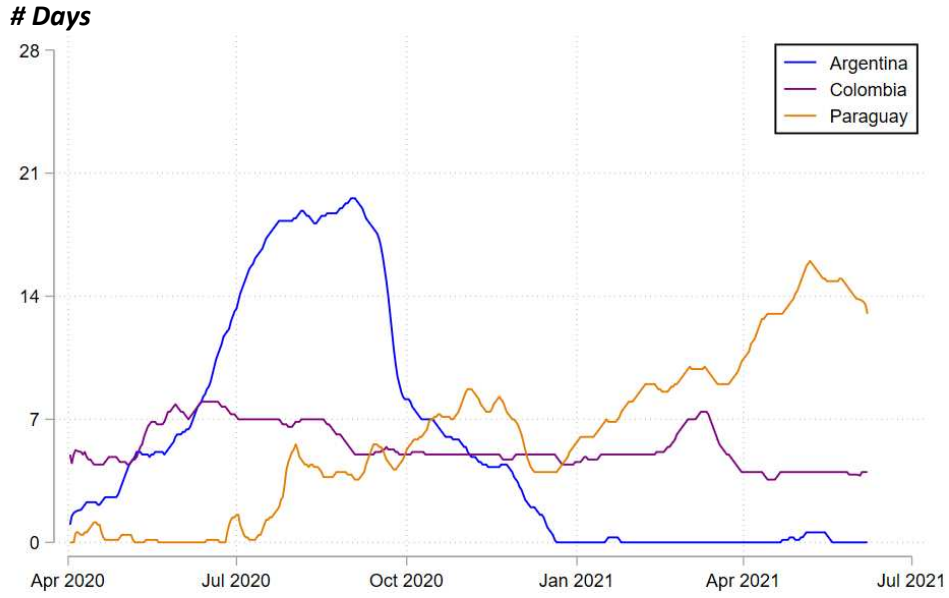
- 7 to 22 days for Argentina (19)
- 9 to 24 days for Colombia (20)
- 10 to 26 days for the Brazilian states of Espírito Santo (21) and Parana (22)

These intervals largely agree with IQRs reported for the USA as:

- 9 to 24 days for ages 18-64
- 7 to 19 days for ages >64 (12)

The IQR for the interval between death and official reporting for the USA was 2 to 19 days (12). This largely matches the interval ranges for Argentina (19), Colombia (20), and Paraguay (23) before March 2021 when included seroprevalence studies stopped collecting samples (see section 1.b), as shown below:

Figure A1 – Death Reporting Lags



Argentina, Colombia, and Paraguay may be outliers with respect to the systematic collection and publication of vital statistics during the pandemic (24); so other developing countries may have substantially longer reporting lags that may not be documented in the absence of detailed case data. The time interval between symptom onset and official death reporting thus appears roughly similar in developing countries as in our previous analysis of high-income countries such as the USA (12).

For some study locations, we were able to extract COVID-19 fatality data from case databases that specified the actual date of death; in those instances, we used the cumulative number of fatalities as of two weeks after the midpoint date of serology specimen collection. In other locations, fatality data was only available from official epidemiological bulletins, in which the official number of cumulative deaths announced at a particular date reflected reporting lags. In those instances, as in

our previous work (12), we extracted death information four weeks after the midpoint of specimen collection. These timing specifications reflect approximate 95th percentiles as follows:

- 2-week interval between symptom onset and seropositivity,
- 4-week interval between symptom onset and death,
- 2-week interval between death and official reporting.

There is also the question of what is the most appropriate death data to use. In most countries there are two sets of COVID-19 deaths: confirmed or suspected. In some countries the government will also present a third tally of deaths, which is modelled using excess mortality statistics or similar. Confirmed COVID-19 deaths may under-estimate the total number of COVID-19 deaths due to insufficient testing (25-28). This may be detected by comparing reported COVID-19 deaths with excess deaths, as reflected in the Peruvian government increasing their tally of reported deaths in a manner that better approximated total excess deaths (24, 29). Nepal's government also later substantially increased their reported tally of COVID-19 deaths (30).

Problems with death reporting are well-illustrated by the case of Mexico, a country whose vital statistics system has notable gaps and which experienced a huge number of COVID-19 deaths. When looking at the raw data on individuals, 90% of those who died did not have a date of death entered into the publicly available data. Previous research also demonstrated that large numbers of people who died from COVID-19 in Mexico failed to access a test and thus are not included in the country's mortality statistics (28). This means that the reported death data available for Mexico is not sufficient to derive a high-quality COVID-19-related IFR. We therefore instead used an alternative official source in Mexico that accounted for this COVID-19 death under-estimation (31).

So for the purposes of the primary analysis, we included the confirmed + suspected death figures where available instead of only confirmed deaths, as confirmed + suspected is the more robust estimate of reported COVID-19 deaths in developing countries. Death data were extracted from national datasets in each country where possible, with alternative sources noted where applicable. Where death data were not immediately available, we contacted the national or local authority through email or social media. We also attempted to confirm death data using the most robust source, and in most cases took the estimate directly from the relevant health authority rather than data aggregation websites. We include our informal assessment of risk of COVID-19 death under-estimation in the appendix folder of our GitHub repository. This is assessment is based on percentage of deaths well-certified in the past decade (32), and on comparison of reported COVID-19 deaths to excess deaths.

e. Assay Characteristics and Seroconversion

For the assays used in the serology studies that were included in our analysis, we catalogued the assay manufacturer's estimates of sensitivity and specificity as well as third-party assessments of its performance characteristics. In addition, we conducted a review to assess serological assays for risk of seroreversion. This review was restricted to studies that tested the same individuals at two different time-points separated by at least two months, or tested individuals at least two months after their first known positive test for SARS-CoV-2. We placed emphasis on commercial assays or assays used in seroprevalence studies.

The search used the terms *"COVID-19 seroreversion"* and *"COVID-19 longitudinal, antibody waning"* in Medrxiv, Biorxiv, Google Scholar, and SSRN. Searches were completed at least monthly from March 2021 to June 2021, with the final search performed on June 30, 2021. We supplemented this with seroreversion studies found during searches up to July 14 for seroprevalence studies with representative sampling, and for which further information was released after July 14 (see "*Systematic Review Methodology*"). Finally, we selected the studies that contained information

about assays that had been used in the serology studies included in our analysis (as described in the preceding subsections of this appendix).

Our systemic review of assay characteristics revealed that the Wondfo assay exhibited extreme variations in test sensitivity across batches, apparently reflecting defects in its manufacturing process (33-35); consequently, any serology study which used this assay was excluded from our analysis.

For seroprevalence to approximate the number of people infected, almost all infected people need to seroconvert by increasing antibody levels after infection. Studies of large populations suggest that >85% or >90% of SARS-CoV-2-infected individuals seroconvert by approximately 2 weeks after infection (36-39). This increases confidence in the accuracy of seroprevalence-based infection estimates that use tests with sufficiently high sensitivity (36, 40, 41). Moreover, >50% of the total population seroconverted in several locations, which would not occur if a substantial proportion of infected individuals failed to seroconvert. Table A1 illustrates this with studies reporting >50% seroprevalence before the onset of widespread SARS-CoV-2 vaccination:

These high seroprevalence estimates may shed light on high vs. low herd immunity thresholds (42-44). For example, Leticia suffered another wave of SARS-CoV-2 infections after reported seroprevalence of 62%, as did Delhi after reported seroprevalence of 56%, the state of Maranhão after reported seroprevalence of 40%, and Jordan after reported seroprevalence of 34% (20, 45, 46). Cross-reactivity also likely does not account for elevated seroprevalence in many of the regions listed in table A1, since cross-reactivity did not significantly reduce test specificity in locations such as Colombia, Ethiopia, and Iran (47-49). These high seroprevalence estimates instead imply that the vast majority of infected individuals seroconverted, increasing the reliability of seroprevalence-based infection estimate (50).

Some serological assays exhibit significantly lower specificity in African populations, possibly due to cross-reactivity with other pathogens (48, 51). This may contribute to divergent seroprevalence estimates between two studies performed in Addis Ababa, Ethiopia (49, 52) (see supplementary appendix section 3.i). However, specificity likely remains high in African populations for many of the assays used in our included studies (49, 53, 54).

Finally, it should be noted that the Gladen-Rogan procedure of adjusting for assay specificity and sensitivity (55)) assumes that those characteristics are precisely known, without accounting for the uncertainty that comes with inferring characteristics from a limited number of tested samples (56). By contrast, our statistical model uses Bayesian methods that incorporate this form of uncertainty.

Table A1 - Locations with Seroprevalence Exceeding 50%

Region	Location	Reported seroprevalence	Number tested for seroprevalence estimate
Latin America	Argentina: Buenos Aires (Barrio Padre Mugica)	53.4% (CI: 52.8 - 54.1%)	873
	Argentina: Metropolitan Area of Buenos Aires (17 de Noviembre)	56.7% (CI: 55.8 - 57.6%)	300
	Colombia, 10 cities: Barranquilla	53% (CI: 41 - 65%)	1426
	Colombia, 10 cities: Guapi	78% (CI: 65 - 91%)	721
	Colombia, 10 cities: Leticia	62% (CI: 51 - 73%)	1417
	Colombia, Córdoba: Montería	55.3% (CI: 52.5 - 57.8%)	1368
	Peru: Iquitos; July, August	70% (CI: 67 - 73%) 66% (CI: 62 - 70%)	716 621
Africa	Ethiopia: Addis Ketema	54.2% (CI: 47.5 - 60.7%)	218
Middle East	Afghanistan: Kabul	53% (CI: < +/-6%)	-
	Iran, 18 cities: Qom, Rasht	58.5% (CI: 37.2 - 83.9%) 72.6% (CI: 53.9 - 92.8%)	108 99
	Iraq: Duhok city	62.6%	743
South Asia	Bangladesh: Dhaka (“slums”)	74%	-
	India: Delhi	56.1% (CI: 55.5 - 56.8%)	28,169
	India: Hyderabad	54.2% (CI: 53.2 - 55.2%)	9363
	India: Karnataka (urban areas)	53.8% (CI: 48.4 - 59.2%)	453
	India: Mumbai, 3 “slums” (in: Chembur West, Dahisar, Matunga)	56.4% 55.1% (CI: 52.4 - 57.8%) 51.1% (CI: 46.4 - 55.8%) 57.0% (CI: 54.7 - 59.2%)	4202 1511 570 2121
	India: Pune, 5 subwards (Lohiyanagar-Kasewadi, Navi Peth-Parvati, Yerwada)	51.3% (CI: 39.9% - 62.4%) 66.4% (CI: 57.8% - 74.1%) 54.1% (CI: 48.3% - 61.7%) 55.5% (CI: 46.6% - 64.1%)	1659 307 331 367

Notes: CI refers to confidence interval. This analysis is restricted to studies with at least 75 people tested. Links to these studies are provided in the Appendix folder of our GitHub repository.

f. Covariates

We extracted data from the most recent year prior to the pandemic, which in most cases was 2019 or earlier. For some estimates such as workforce, we relied on the best available data, some of which was several years old for some countries.

The covariates are:

1. GDP per capita
2. Healthcare spending
3. GNI per capita
4. Hospital beds per capita
5. Life expectancy at birth
6. Healthy life expectancy at age 60
7. Global health security index
8. Skilled healthcare workers per capita
9. Universal health coverage index
10. % of deaths well-certified (32)

Briefly, these covariates were chosen because they either relate to the expected quality of the health system itself (i.e. doctors/nurses per population) or to how likely a country was to be accurately recording the burden of COVID-19 (WHO indicators, human development index). We also included the ratio of life expectancy between age 60 and 20 to account for the potential for survivorship bias – if there was a significant element of survivorship bias in the countries examined, we would expect the ratio to be higher as more elderly people survived longer periods in places with higher mortality in youth.

2. Statistical Methodology

a. Adjustment for Seroreversion

Seroreversion occurs when the specific antibodies a serological assay tests decline to below the assay's level of detection, preventing the assay from identifying infected individuals. As many studies conducted in developing countries were performed long after initial COVID-19 waves passed, the risk of seroreversion could be high. This could lead to underestimation of the proportion of infected people and thus unreliable estimates in our computed IFRs. Moreover, any modelling using assumptions about seroreversion for one serological test would almost certainly lead to errors in other places as different tests can substantially differ in characteristics (57).

For all other assays that were used in the serology studies included in our analysis, we classified each assay's risk of seroreversion (high, medium, or low) based on two sources of data:

- *Longitudinal serology studies*, in which specimens were collected periodically from a given sample of individuals over an extended period of time.
- *Serology analysis of prior RT-PCR positive cases*, i.e., collection of specimens from individuals who had previously tested positive for COVID-19.

Some seroprevalence studies tested a representative sample of the general population, including those with a prior positive SARS-CoV-2 PCR test weeks or months before serological testing, a previous COVID-19 diagnosis weeks or months before serology, etc. If many of these prior-positive individuals later tested seronegative, then that is unlikely to represent failed seroconversion, as previously discussed. It instead likely indicates a high risk of seroreversion during the time following their initial positive test (58). A threshold of <75% sensitivity was selected for this risk of seroreversion because at least 75% of prior-positives tested seropositive using the Roche assay that is at low risk of seroreversion (see Table A2), and the vast majority of sources reported sensitivity of at least 75% before seroreversion, as shown in the input data of our GitHub repository.

Table A2 indicates our assessment of the seroreversion risk of each assay for which sufficient information was available from longitudinal data or analysis of prior confirmed RT-PCR positive cases. For each assay, this table also shows the locations for which we have estimated IFR from serology results obtained using that assay.

Although not shown in the table, three of these assays were also used to estimate seroprevalence in *"Sero-Only"* locations where IFR could not be estimated due to lack of corresponding fatality data: (1) *Roche Elecsys (anti-nucleocapsid)* was used in Duhak, Iraq; Hyderabad and Rourkela, India; Gaza and West Bank, Palestine; and Jourberton, South Africa. (2) *Euroimmun IgG* was used in Tirana, Albania; Pune, India. (3) *Wantai IgG/IgM* was used in Cox's Bazar Rohingya camps, Bangladesh; Georgia *(4 districts)*; Malaysia *(nationwide)*; Mongolia *(nationwide)*, Klerksdorp & Pietermaritzburg, South Africa; and Phuket, Thailand.

For every location for which the assay used in serology was classified as having high risk of seroreversion, we made corresponding adjustments to the data on assay sensitivity as follows:

- *Abbott Architect assay.* We used information from prior studies to assess how the sensitivity of this assay diminishes over time following the onset of infection at each monthly interval from 0 to 6 months. For each of the seven locations where this assay was used, we

computed its weighted sensitivity as of the midpoint date of the serology study, where the weights were determined by the time path of confirmed SARS-CoV-2 cases in that location.

- *Other assays with high risk of seroreversion*. For each of the three locations that used such assays, we extracted information about the seropositivity of specimens from individuals with a prior positive RT-PCR test. This approach automatically accounts for the variation in time intervals since infection, because each of these serology studies used a representative sample of the general population, and is consistent with prior work on how waning of antibodies reduces the proportion of prior-positives who test seropositive (58, 59).

Table A2 – Seroreversion Assessments and Sources

Risk Category	Assay	IFR Locations	Seroreversion Data: *Sequential Tests*	Seroreversion Data: *Prior Positives*	Citations
High	Abbott Architect IgG	Ethiopia: *Dire Dawa*	X		(37, 60-70)
		Hungary *(nationwide)*	X		
		Bosnia & Herzegovina: *Republika Sprska*	X		
		India: *Chennai, Mumbai, Pimpri-Chinchwad, Srinagar*	X		
	ErbaLisa IgG	India: *Paschim Medinipur*		X	(71, 72)
	Zydus Kavach IgG	India: *Delhi*		X	(71)
	Luminex S	South Africa: *Gauteng*		X	(58)
Moderate	Euroimmun IgG	Zambia: *Lusaka & Ndola*	X	X	(67, 73-77)
		Poland: *Katowice*	X		
	Roche Elecsys IgG/IgM *(anti-nucleocapsid)*	Brazil: *Maranhao, Sao Paulo*	X		(37, 38, 64, 69, 70, 73, 78-83)
		Chile: *3 urban areas*	X	X	
		India: *Berhampur, Bhubaneswar, Puducherry*	X	X	
		Mexico *(nationwide)*	X	X	
		Pakistan: *Karachi, Lahore*	X		
Low	COVIDAR IgG	Argentina: *Buenos Aires City, Hurlingham*	X		(84, 85)
	DiaSorin Liaison IgG	Brazil: *Cuiabá, Mato Grosso, Pitangueiras, Várzea Grande*	X		(37, 57, 60, 69, 70, 86)
		Oman *(nationwide)*	X		
	Genetico CoronaPass Total	Russia: *St. Petersburg*	X		(63, 65)
	Ortho Vitros IgG	India: *Tamil Nadu*	X		(57)
	Roche Elecsys IgG/IgM *(anti-spike)*	N/A	X		(64, 87)
	Siemens Advia IgG/IgM	Colombia: *Barranquilla, Bogotá, Bucaramanga, Cali, Cucuta, Ipiales, Leticia, Medellin, Villavicencio*	X		(69, 70)
	University of Rio de Janeiro	Brazil: *Rio Grande do Sul*	X		(33, 88)
	Wantai SARS-CoV-2 Total	Jordan *(nationwide)*	X		(64, 89, 90)
		Kenya: *Nairobi*	X		
		Nepal *(nationwide)*	X		
		Senegal *(nationwide)*	X		
		South Africa: *Mitchells Plain*	X		

Note: *This table shows the seroreversion risk category assigned to each assay for which sufficient information was available.*

- *Assays with medium risk of seroreversion*. For locations that used either of these assays, we extracted information about the seropositivity of specimens from individuals with a prior positive RT-PCR test, and we utilized that data if the seropositivity rate was less than 75% (corresponding to a significant degree of seroreversion in that location.)

Given the seroreversion-adjusted sensitivity for each location, we imputed the corresponding number of seropositive specimens that would be obtained using the actual sample size for that serology study, and then those values serve as inputs to the Bayesian model described below. This approach is conceptually similar to prior studies that have imputed the number of specimens and the number of confirmed cases by inverting seroprevalence confidence intervals (10, 91).

Finally, Table A3 lists the assays for which seroreversion could not be assessed due to insufficient information. For each assay, this table shows the IFR and "Sero-Only" locations for which we relied on the baseline characteristics of that assay.

Table A3 – Assays with Unknown Seroreversion

Assay	IFR Locations	Sero-Only Locations
Abbott PanBio IgG/IgM	Mozambique: *Maputo*	Mozambique: *Beira, Chókwè, Matola, Quelimane, Xai-Xai* Pakistan: *Islamabad*
Beijing Kewei IgG/IgM	Paraguay: *Asuncion & Central Dept.*	
Bioscience IgG/IgM	China: *Wuhan, Hubei ex. Wuhan*	China: *3 provinces*
Core Technology IgG	Ethiopia: *Addis Ababa*	Ethiopia: *3 towns*
Coretest IgG/IgM	Peru: *Lambayeque*	
CTK Biotech Onsite IgG/IgM	Brazil: *Distrito Federal*	
ECO IgG/IgM	Brazil: *Pitangueiras*	
GenBody IgG		Dominican Republic: *10 provinces*
Healgen IgG/IgM		Yemen: *Aden*
INgezim DR IgG/IgM/IgA	Colombia: *Córdoba*	
Karwa Kavach IgG	India: *Malegaon*	India: *Indore, Jabalpur*
Luminex N		Dem. Rep. of Congo: *Kinshasa*
Orient Gene Biotech IgG/IgM	Brazil: *Iquitos, Loreto*	
Pishtaz Teb IgG/IgM	Iran *(nationwide)*	
Proprietary assay #1	Brazil: *Foz do Iguaçu*	
Proprietary assay #2		Laos: *5 provinces*
Proprietary assay #3		Zimbabwe: *Budiriro & Highfield*
Proprietary assay #4		South Sudan: *Juba*
Qingdao Hightop IgG/IgM		Mozambique: *Chimoio, Tete, Massinga, Maxixe, Pemba*
RightSign IgG/IgM		Libya: *Benghazi*
Shenzhen iFlash IgG	India: *Tamil Nadu* Ecuador: *Cuenca*	
Standard Q IgG/IgM	Peru: *Lima & Callao* Bolivia: *Santa Cruz*	Mozambique: *Nampula*
THSTI IgG	India: *Karnataka*	
UNCOV-40 IgG/IgM		Nigeria: *Niger State*

b. Bayesian Model for Estimating Seroprevalence and IFR

Model for COVID-19 infections

Let $R^{\star}_{\mathrm{l},A}$ be the number of individuals who tested seropositive in age group *A* at location l, and $n_{\mathrm{l},A}$ give the number of individuals tested in that age group for this location. We model the number of individuals with a positive serology test in the study as

$$R^{\star}_{\mathrm{l},A} \sim \text{Binomial}\left(n_{\mathrm{l},A}, p_{\mathrm{l},A}\right), \text{ where} \tag{1}$$

$$p_{\mathrm{l},A} = \text{sens}_{t_{\mathrm{l}}}\pi_{\mathrm{l},A} + \left(1 - \text{spec}_{t_{\mathrm{l}}}\right)\left(1 - \pi_{\mathrm{l},A}\right). \tag{2}$$

To account for the error rates of the test, the test positivity probability, $p_{\mathrm{l},A}$, is defined as a function of test sensitivity ($\text{sens}_{t_{\mathrm{l}}}$), test specificity ($\text{spec}_{t_{\mathrm{l}}}$), and the true seroprevalence ($\pi_{\mathrm{l},A}$) for the associated location and age group at the time of the study. For many studies, we did not have seropositivity by age, in which case *A* represented all ages.

To account for uncertainty in the test characteristics, we model the lab validation data directly. Let $n_{\text{sens},t}$ denote the number of positive specimens tested with test *t*, and $x_{\text{sens},t}$ the number of positive specimens that correctly tested positive. Similarly, let $n_{\text{spec},t}$ and $x_{\text{spec},t}$ denote the number of negative specimens tested and the number of negative specimens that correctly tested negative with test *t*, respectively. We model these quantities as follows:

$$x_{\text{sens},t} \sim \text{Binomial}(n_{\text{sens},t}, \text{sens}_t) \tag{3}$$

$$x_{\text{spec},t} \sim \text{Binomial}(n_{\text{spec},t}, \text{spec}_t). \tag{4}$$

Model for COVID-19 deaths

Let $D^{\star}_{\mathrm{l},A}$ give the number of recorded COVID-19 deaths, for age group *A* at location l. Note that if only a single death record is available, then *A* represents the entire age range. We model the recorded COVID-19 deaths as

$$D^{\star}_{\mathrm{l},A} \sim \text{Poisson}\left(N_{\mathrm{l},A} \times \pi_{\mathrm{l},A} \times \text{IFR}_{\mathrm{l},A}\right) \tag{5}$$

where $N_{\mathrm{l},A}$ gives the number of individuals at location l in age group *A*. Then $N_{\mathrm{l},A} \times \pi_{\mathrm{l},A}$ gives the expected number of infected individuals, and $\text{IFR}_{\mathrm{l},A}$ is the infection fatality rate for location l and age group *A*, representing the probability an individual dies from COVID-19, given the individual had COVID-19. Note, the Poisson distribution reflects the relative rarity of a COVID-19 fatality relative to the entire population.

Accounting for data collected in varying age bins

Notice that the models above for deaths and infections in (1) and (5) are functions of prevalence and IFR, respectively, defined on discrete age bins. However, the discrete age bins are not necessarily the same for the death data and the seroprevalence studies. The following adjustments were made to match serology and death age bins:

- **Death bins nested within a serology bin:** We aggregate deaths for each location to match the respective serology age bins to avoid placing assumptions about the variability of prevalence across ages within a single serology age bin.
- **Serology bins nested within a death bin:** The average seroprevalence for the death age bin is calculated as an average of the serology age bins, weighted by the percent of the population in each age bin.

- **Bin endpoints slightly off:** When age bins were within one or two years of matching, serology age bins were adjusted to match the corresponding death age bins.

All modifications to age bins are documented in a spreadsheet in the data folder.

Population Age Distribution

Let $f_l(a)$ denote the number of individuals of age *a* at location l for *a* ∈ (0,1,...,84+). Note, if population age structure is only available in 5 year age bins, then define

$$f_l(a) = \sum_{b\in[0,5,\ldots,80]} \frac{f_l\big([b,b+5)\big)}{5} I_{[b,b+5)}(a)$$

where $f_l\big([b,b+5)\big)$ is the proportion of the population ages $[b,b+5)$.

In cases where the location specific age structure is only available in large bins, but the national age structure is available in 5 year age bins, we leverage the national age structure to inform the location specific age structure as follows. Let *A* denote an interval the location specific age structure is available for (e.g., [0,18)). If *f*(*A*) is the proportion of the population at location l with an age in *A* and $f_n(a)$ is the proportion of the population aged *a* at the national level, then we estimate $f_l(a)$, the proportion at location l that is age *a*, as

$$f_l(a) = f(A)\frac{f_n(a)}{\sum_{b\in A\cap N} f_n(b)}. \quad (6)$$

Essentially, we rescale $f_n(a)$ such that the total mass in *A* matches the observed total mass in *A* at location l, *f*(*A*). Since we model seroprevalence as constant past age 85, we let $f_l(85)$ represent the proportion of the population aged 85 or older, rather than just the proportion aged 85.

Calculating Average Seroprevalence within a Death Age Bin

Define the population age density for age bin *A* as

$$f_{l,A}(a) = \frac{f_l(a)}{\sum_{b\in A\cap N} f_l(b)},\ a \in (0,1,\ldots,84+) \quad (7)$$

in order to truncate $f_l(a)$ to age bin *A*.

The prevalence for age bin $B = \cup_{A\in\mathcal{A}} A$ is then defined

$$\pi_{l,B} = \sum_{A\in\mathcal{A}}\big[\pi_{l,A}\sum_{b\in A\cap N} f_{l,A}(b)\big]. \quad (8)$$

For the locations where we only have serology study information with no corresponding fatality data, the proportion of all study participants that were in a given age bin was assumed representative of the proportion of the population in each age bin since the studies were designed to have representative samples. For the locations with both serology and fatality data, population data were recorded in the Population Distributions tabs with citations.

Priors

Because there are infinitely many combinations of prevalence, sensitivity, and specificity that can result in the same test positivity rate, we used weakly informative priors for the seroprevalence parameters and informative priors for sensitivity and specificity to avoid a multimodal posterior, similar to Gelman and Carpenter (2020). For the seroprevalence parameters, $\pi_{l,A}$, we used independent, weakly informative priors:

$$\pi_{l,A} \sim \text{Beta}(2,6) \quad \text{for all l}, A. \tag{9}$$

These priors assume a mode around 0.15 with a prior probability of 0.8 that $\pi_{l,A}$ falls between 0 and 0.8.

We also used independent priors for the test sensitivities and specificities. For each test assay *t*, the priors on the sensitivity and specificity were

$$\text{sens}_t \sim \text{Beta}(10,1) \tag{10}$$

$$\text{spec}_t \sim \text{Beta}(50,1). \tag{11}$$

To further narrow the seroprevalence, sensitivity, and specificity combinations, we used independent, mildly informative priors for each IFR parameter based on expert knowledge. IFR for COVID-19 is known to increase with age. We also expect IFR to be more extreme (smaller than average or larger than average) when the age bin is small. For example, we would expect an age bin from 20-80 to look similar to the country average, but we would expect an age bin from 70-80 to be much higher than the country average. To formulate a prior that reflects these characteristics, we modeled

$$\text{IFR}_{l,A} \sim \text{Beta}\left(1, \text{IFR}_{l,A}^{\text{prior}}\right) \tag{12}$$

where

$$\text{IFR}_{l,A}^{\text{prior}} = 30 - 20\left[\frac{U_{l,A}-50}{50}\left(1 - \frac{U_{l,A}-L_{l,A}}{100}\right)\right]. \tag{13}$$

The lower and upper bounds of age bin *A* at location l are given by $L_{l,A}$ and $U_{l,A}$, respectively. For open-ended upper ages, we set $U_{l,A} = 100$. As an example, $\text{IFR}_{l,[0,100)}^{\text{prior}} = 30$, while $\text{IFR}_{l,[80,100)}^{\text{prior}} = 14$, allowing for larger IFR estimates when focusing on the older individuals.

Model Implementation

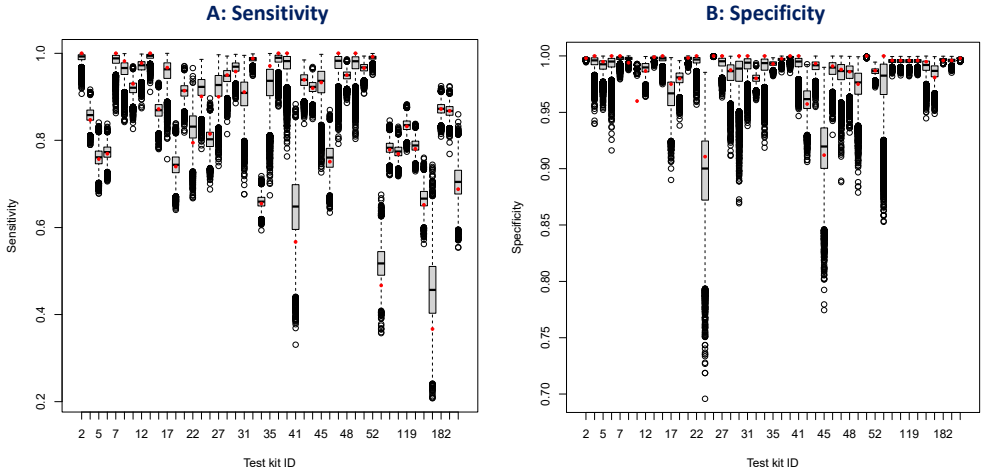
The model was implemented in version 4.0.2 of the programming language R, and posterior samples were obtained via the software package Stan (version 2.21.1). We ran three chains for 10,000 iterations, where the first 5,000 iterations were discarded as warm-up samples. All parameters had an effective sample size greater than 1,200. Additionally, the $\hat{R}$ value was within 0.0016 of 1 for each parameter, suggesting convergence. Examination of traceplots also suggested convergence.

Out-of-sample observation were run as a separate model, so information on test sensitivity and specificity was not pooled between in-sample observations and out-of-sample observations. Traceplots, effective sample size (minimum of 2100), and $\hat{R}$ values (within 0.0029 of 1) suggested convergence of the out-of-sample model as well.

We compared plugin estimates for parameters to the posterior distribution for each parameter to check model fit. In each case there was good agreement, or the Bayesian estimate was superior. For example, in Figure A2, we compare the posterior distribution of the sensitivity and specificity estimates to the raw estimate. In most cases, the middle 50% of the posterior distribution contains

the raw estimate. However, for test kit ID 11 (Qingdao Hightop Biotech IgM/IgG Duo), the raw estimate of specificity is outside the range of the posterior draws. In the case of this test, it was used in locations with extremely low prevalence, such that the Gladen-Rogan (55) adjustment results in a negative estimate of prevalence (meaning the expected number of false positives is greater than the number that tested positive.) Since this is unreasonable, the Bayesian model raises the specificity estimate, lowering the expected number of false positives.

Figure A2 – Sensitivity and Specificity Posterior Distributions



Note: These boxplots show the posterior distribution of each assay's sensitivity (panel A) and specificity (panel B) compared to the raw estimate (red dot) based on lab validation data. Further details (including the name of each assay) are given in the appendix folder of our GitHub repository.

Model Outputs

For each model parameter, we use the posterior mean as the point estimate and produce 95% equal-tail credible intervals to describe uncertainty.

Total seroprevalence

Similar to calculating the average seroprevalence for a death age bin, we estimate total seroprevalence for a location by taking an average of the age bin seroprevalences, weighting by the population distribution at that location:

$$\pi_{l,[0,100+)} = \sum_{A \in \mathcal{A}_\ell} \left[\pi_{l,A} \sum_{b \in A \cap N} f_{l,A}(b) \right] \quad (14)$$

where $\mathcal{A}_\ell$ are the serology age bins associated with location l.

Assessing Uniformity of Seroprevalence Across Age

We calculated total seroprevalence for younger adults and middle aged adults, compared to older adults. The age bins used for each location were selected as follows:

- **Younger adults (approximately 18 to 59):** Any age bins such that 15 ≤ lower age < 60 and 20 < upper age ≤ 65 were included

- **Middle aged adults (approximately 40 to 59):** Any age bins such that 40 < lower age < 60 and 40 < upper age ≤ 65 were included
- **Older adults (approximately 60 and older):** Any age bins such that 60 ≤ lower age were included.

This resulted in sets of bins where the 18-59 bins and the 40-59 bins did not overlap the 60+ bins.

We then calculated total seroprevalence from age *a* to *b* using appropriate age bins, $\mathcal{A}$, similar to equation (8)

$$\pi_{l,a-b} = \sum_{A\in\mathcal{A}} \pi_{l,A} \frac{n_{l,A}}{\sum_{B\in\mathcal{A}} n_{l,B}} \quad (15)$$

where $\frac{n_{l,A}}{\sum_{B\in\mathcal{A}} n_{l,B}}$ estimates the percent of the total population in that age bin, assuming representative age distributions in the serology studies.

For each draw from the posterior distribution, we calculated $\pi_{l,a-b}$ for each of our three age intervals of interest. We then calculated the ratios $\frac{\pi_{l,60+}}{\pi_{l,18-59}}$ and $\frac{\pi_{l,60+}}{\pi_{l,40-59}}$ for each draw.

Total IFR and Comparison to High-income (EJE) Prediction

Total IFR

Suppose location l has death age bins $\mathcal{A}_\ell$. Let $\sum_{b\in A\cap N} f_{l,A_i}(b) = \text{pop}_{l,A}$ for $A \in \mathcal{A}_\ell$. Then

$$\begin{aligned}\text{IFR}_{\text{total}} &= \frac{\text{number of deaths}}{\text{number of infections}} \\ &= \frac{\sum_{A\in\mathcal{A}_\ell} \text{IFR}_{l,A} \times \pi_{l,A} \times \text{pop}_{l,A}}{\sum_{B\in\mathcal{A}_\ell} \pi_{l,B} \times \text{pop}_{l,B}} \\ &= \sum_{A\in\mathcal{A}_\ell} \text{IFR}_{l,A} \times \left(\frac{\pi_{l,A}\times\text{pop}_{l,A}}{\sum_{B\in\mathcal{A}_\ell} \pi_{l,B}\times\text{pop}_{l,B}}\right) \quad (16)\end{aligned}$$

estimates the total IFR for location l. By calculating $\text{IFR}_{\text{total}}$ for each posterior sample, we can then obtain posterior mean and credible intervals for $\text{IFR}_{\text{total}}$.

High-income country benchmark

We compare the IFR estimate to a high income country benchmark based on results from Levin et. al. (4) which found a log-linear relationship between age and IFR. Define

$$\text{HICB}_a = \begin{cases} \int_a^{a+1} \frac{1}{100} 10^{-3.27+0.0524a} da & \text{if } a < 85 \\ \frac{1}{100} 10^{-3.27+0.0524(85)} & \text{if } a \geq 85 \end{cases}. \quad (17)$$

Then HICB_a represents the IFR predicted by the high-income countries line averaged over the interval [*a*,*a*+ 1) for ages less than 85 and assumes the high-income countries line flattens out and becomes uniform for ages 85 and older.

Then if we assume uniform prevalence for a location, the total IFR estimate over age bin *A* for high-income countries is

$$\text{HICB}_A = \frac{\sum_{a\in A} \text{EJE}_a \times f_l(a)}{\sum_{b\in A} f_l(b)}. \quad (18)$$

Subsetting to ages 18-65

To estimate the IFR between ages 18 and 65, we used the same strategy in picking age bins as we did when testing uniform prevalence. That is, we selected $\mathcal{B}_\ell$ to be the death age bins in $\mathcal{A}$ such that the lower age of the bin is greater than or equal to 18 and the upper age of the bin is less than 66. We then applied equation (16), replacing $\mathcal{A}_\ell$ with $\mathcal{B}_\ell$. We were not able to calculate the IFR between 18 and 65 for locations there were no age bins in $\mathcal{B}_\ell$.

Baseline population

In order to compare the impact of the age specific IFR while controlling for population age distribution, we calculated the Total IFR substituting $f_{\mathrm{l}}(a)$ for a baseline population age distribution, $\bar{f}(a)$ in (16). We calculated $\overline{f_A}(a)$ following (7). The baseline population was calculated as a median across locations for each age, then rescaled to sum to one:

$$\overline{f_\star}(a) = \text{median}\{\, f_{\mathrm{l}}(a) \mid \mathrm{l} \text{ is one of the observed locations with fatality data} \,\} \tag{19}$$

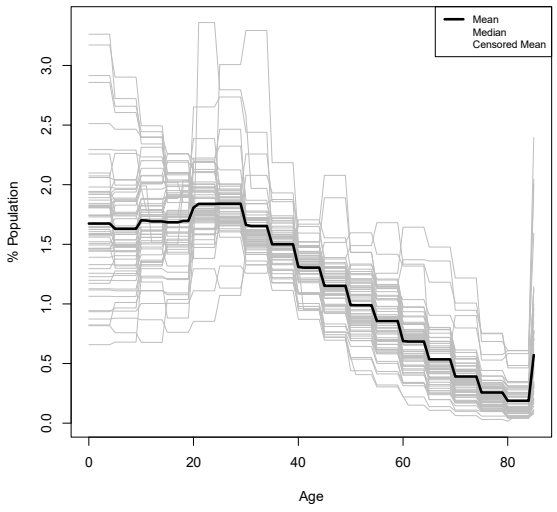
$$\bar{f}(a) = \frac{\overline{f_\star}(a)}{\sum_{a=0}^{85} \overline{f_\star}(a)}. \tag{20}$$

We also considered taking the mean across locations for each age and taking the mean across locations for each age after removing the top five and bottom five locations for that age (a censored mean). All three approaches gave similar values as shown in Figure A3.

Baseline age distribution

Various estimates of baseline age distribution (mean, median, and censored mean) plotted on age distribution for observed locations in grey:

Figure A3 – Estimates of Baseline Age Distribution



Country average

To get an average total IFR estimate for each country, we took a weighted average of the total IFR estimate of the locations within that country. We chose to weight by $1/\sqrt{n_{\mathrm{l}}}$ in order to give more weight to locations with more certain seroprevalence estimates. In locations with multiple age bins, we took the average across $n_{\mathrm{l},A}$ as n_{l}. We weighted by certainty in the seroprevalence estimates rather than the IFR estimates because larger IFR estimates tend to be due to small seroprevalence

estimates and consequently have more uncertainty (i.e., small differences in the denominator, seroprevalence, can result in large changes in the IFR estimate when seroprevalence is small). We did not want to bias the average by down weighting all of the larger IFR estimates.

We followed the same process to estimate the country average IFR between 18 and 65, with the added step of removing any locations in the country where $\mathcal{B}_\ell$ was empty.

c. National Serology Studies of High-Income Countries

As shown in Table A4, many high-income countries succeeded in limiting SARS-CoV-2 transmission during 2020 and early 2021 (92-94). Japan and South Korea (as well as several other East Asian countries) were particularly successful at limiting infection rates (95, 96). Some subnational high-income country locations reported higher seroprevalence, e.g., about 21% in New York City, USA (97), up to 25% in some Swiss cantons (59), and 42% at an Austrian ski area (18). However, the available serology data, based on representative samples of the general population, indicates that no location in any high-income country experienced non-vaccine-induced seroprevalence above 45% prior to March 2021.

Table A4 –National Seroprevalence Estimates for High-Income Countries

Timeframe	Location	Reported seroprevalence	Midpoint date
April 2020 to	Slovenia	0.9% (CI: 0.4-1.4%)	April 25
Sept. 2020	Spain	5.0% (CI: 4.7-5.4%)	May 4
	France	4.5% (CI: 3.9 - 5.0%)	May 17
	Italy	2.5% (CI: 2.3 - 2.6%)	June 19
	United Kingdom	6.0% (CI: 5.8 - 6.1%)	July 1
	Canada	1.9% (CI: 1.4 - 2.0%)	July 15
	South Korea	0.01%	July 19
	Germany	0.7%	July 21
	Denmark	2.0% (CI: 1.7-2.4%)	Sept. 19
	Netherlands	4.7% (CI: 4.0-5.5%)	Sept. 28
Oct. 2020 to	USA	11.9% (CI: 10.5 - 13.5%)	Oct. 30
January 2021	England	5.6% (CI: 5.4-5.7%)	Nov. 3
	Germany	1.1% (CI: 0.9 - 1.3%)	Nov. 6
	Slovenia	4.1% (CI: 3.0 - 5.2%)	Nov. 11
	Austria	4.7% (CI: 3.8 - 5.6%)	Nov. 13
	South Korea	0.1%	Nov. 21
	Spain	9.9% (CI: 9.4 - 10.4%)	Nov. 22
	France	6.2% (CI:5.9-6.6%)	Nov. 26
	Denmark	4.1% (CI: 3.1 - 4.9%)	Dec. 16
	Norway	0.9% (CI: 0.7 - 1.0%)	Jan. 5

Table A5 – Variants of Benchmark Metaregression for High-Income Countries

Description	# Observations	Intercept	Slope Coefficient
Benchmark	104	-3.27 *(0.073)*	0.0524 *(0.0013)*
Exclusion of Convenience Samples	68	-3.32 *(0.089)*	0.0532 *(0.0015)*
Adjustment for Seroreversion	104	-3.22 *(0.070)*	0.0516 *(0.0012)*
Adjustment for Death Undercounting	104	-3.18 *(0.075)*	0.0526 *(0.0013)*

d. Metaregression benchmark for high-income countries

To provide a benchmark for our analysis of IFR in developing countries, we consider the findings from a prior meta-analysis of age-specific IFRs for high-income countries (12). That study conducted a metaregression using 104 observations on age-specific IFRs from 28 locations (using samples collected between April and July 2020) and obtained the following results:

$$\underset{}{log_{10}(IFR)} = \underset{(0.07)}{-3.27} + \underset{(0.0013)}{0.0524 * age}$$

where the standard error for each estimated coefficient is given in parentheses.

To determine whether those results can serve as a suitable benchmark, we must consider several distinct methodological issues. First, the prior study used serology data from convenience samples as well as from representative samples of the general population, whereas our present analysis excludes convenience samples. Second, the prior study computed assay-adjusted seroprevalence using the baseline characteristics of each assay, whereas our present analysis incorporates adjustments for seroreversion over time. Third, the prior study used official reports on confirmed COVID-19 deaths, without incorporating any information about underreporting of COVID-19 fatalities, but subsequent analysis has shown that such underreporting has been substantial in some locations in high-income countries.

To assess the significance of these methodological issues, we have replicated the prior metaregression analysis along with three variants. In the first variant, the metaregression excludes 36 observations from convenience samples. In the second variant, we make seroreversion adjustments for two locations (Italy and Spain) that utilized the Abbott Architect assay, using the same approach as in our present analysis described above. In the third variant, we adjust fatalities using IHME estimates of COVID-19 death undercounts. Table A5 reports the results of this sensitivity analysis. Evidently, the results for each variant are nearly identical to those of the prior benchmark regression, with no statistically significant differences in the estimates of the intercept or slope coefficient. These results underscore the robustness of this metaregression for high-income countries and support its use as a benchmark for assessing IFR in developing countries.

3. Additional Results

a. Seroreversion Estimates

Table A6: Seroreversion Adjustments and Assay Sensitivity

Country	*Location*	*Assay*	*Baseline (%)*	*Adjusted (%)*	*Ratio*
Chile	3 urban areas	*Elecsys*	99.5	68.8	0.69
Ethiopia	Diredawa	*Abbott*	100	86.8	0.87
Hungary	National	*Abbott*	100	87.2	0.87
India	Delhi	*Kawach*	92.1	65.2	0.71
	Pimpri-Chinchwad	*Abbott*	100	77.9	0.78
	Paschim Medinipur	*Erbalisa*	98.3	36.7	0.37
	Chennai	*Abbott*	100	83.2	0.83
	Srinagar	*Abbott*	100	78.1	0.78
	Mumbai	*Abbott*	100	76.9	0.77
South Africa	Gauteng	*Luminex*	100	46.7	0.47

Note: This table shows the characteristics of the assay used in the serology study of each of the specified locations, including the assay sensitivity at baseline, the seroreversion-adjusted sensitivity, and the ratio of adjusted to baseline sensitivity. In denoting these assays, *Elecsys* refers to the Elecsys Anti-SARS-Cov-2 Roche assay, *Abbott* refers to the Abbott Architect IgG assay, Kavach refers to the Kawach IgG assay, *Erbalisa* refers to the ErbaLisa IgG assay, and *Luminex* refers to the Luminex protein trimer assay.

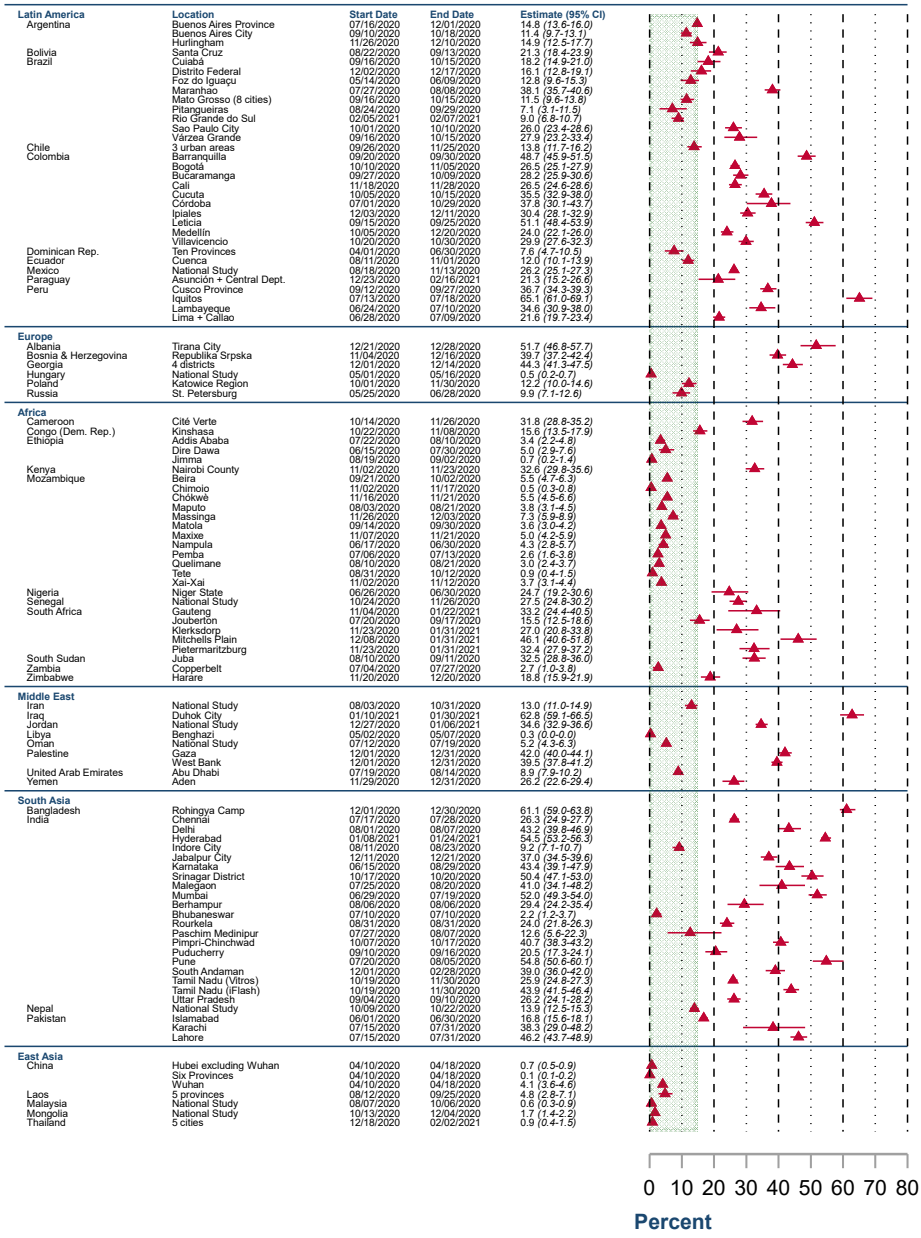
Table A7: Implications for Seroprevalence and IFR

		Seroprevalence (%)			
Country	*Location*	*Baseline Sensitivity*	*Seroreversion-Adjusted Sensitivity*	*Seroprevalence Ratio*	*IFR Ratio*
Chile	3 urban areas	10.1	13.8	1.4	0.73
Ethiopia	Diredawa	4.4	5.0	1.2	0.87
Hungary	National	0.4	0.5	1.4	0.79
India	Delhi	31.2	43.2	1.4	0.72
	Pimpri-Chinchwad	32.9	40.7	1.2	0.83
	Paschim Medinipur	6.8	12.6	1.9	0.55
	Chennai	22.1	26.3	1.2	0.84
	Srinagar	40.2	50.4	1.3	0.80
	Mumbai	40.1	52.0	1.3	0.78
South Africa	Gauteng	18.8	33.2	1.8	0.56

Note: For each location, this table reports the seroprevalence estimate obtained using the baseline sensitivity of the assay used in that serology study as well as the corresponding estimate obtained using the seroreversion-adjusted sensitivity for that assay. The penultimate column shows the ratio of seroreversion-adjusted to baseline-adjusted seroprevalence, while the final column shows the ratio for the corresponding estimates of population IFR for that location.

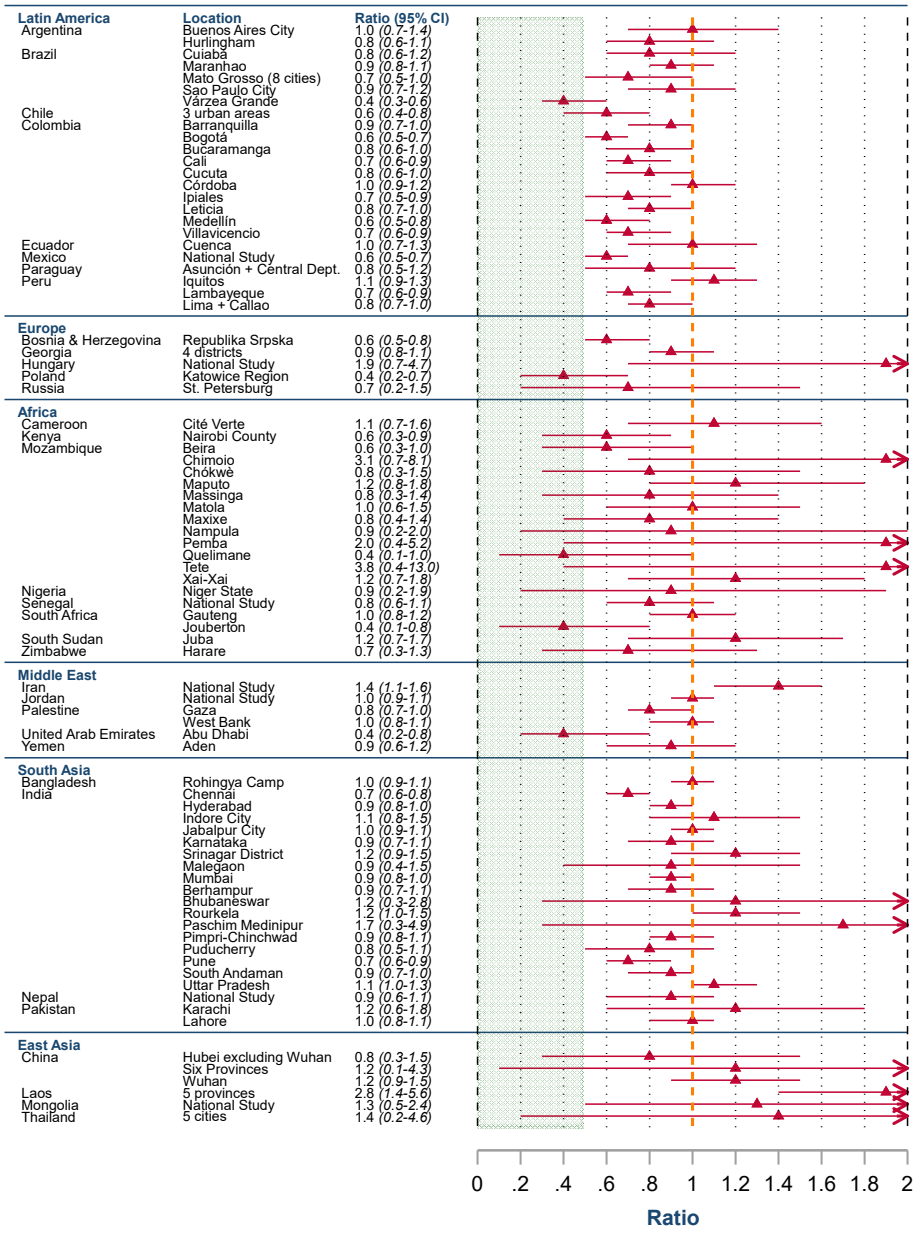
b. Seroprevalence Estimates

Figure A4 – Population-wide Seroprevalence



Notes: The green shading represents the range of national seroprevalence for high-income countries in Table A4. Links to these studies are in the Appendix folder of our GitHub repository.

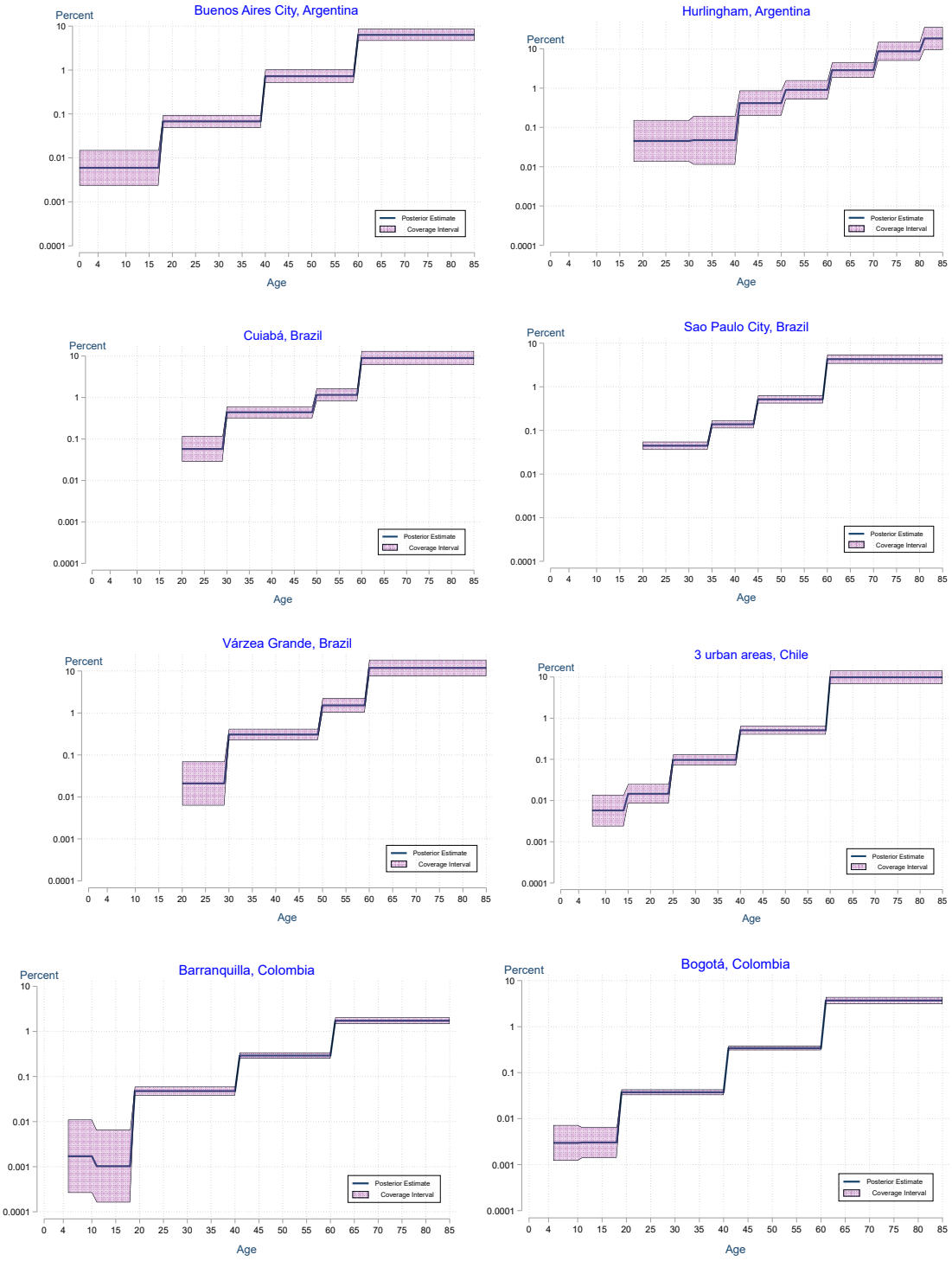
Figure A5 – Ratio of Seroprevalence for Older Adults (60+ years) Compared to Younger Adults (18-59 years)



Note: The green shading represents the range of national seroprevalence for high-income countries from our prior work (12). Links to these studies are in the Appendix folder of our GitHub repository.

c. Age-specific IFR curves by location

Figure A6 – Age-Specific IFR Curves By Location



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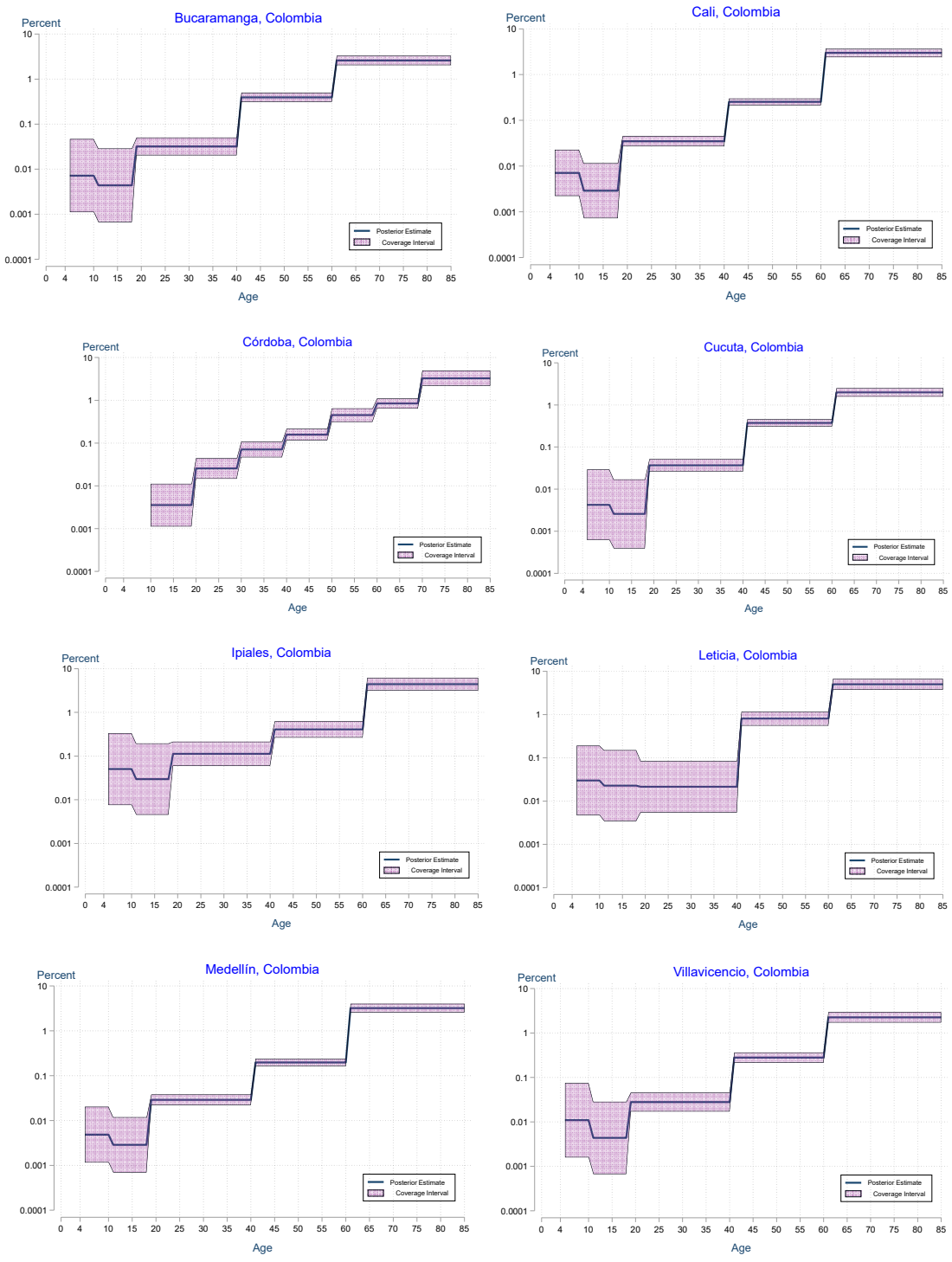

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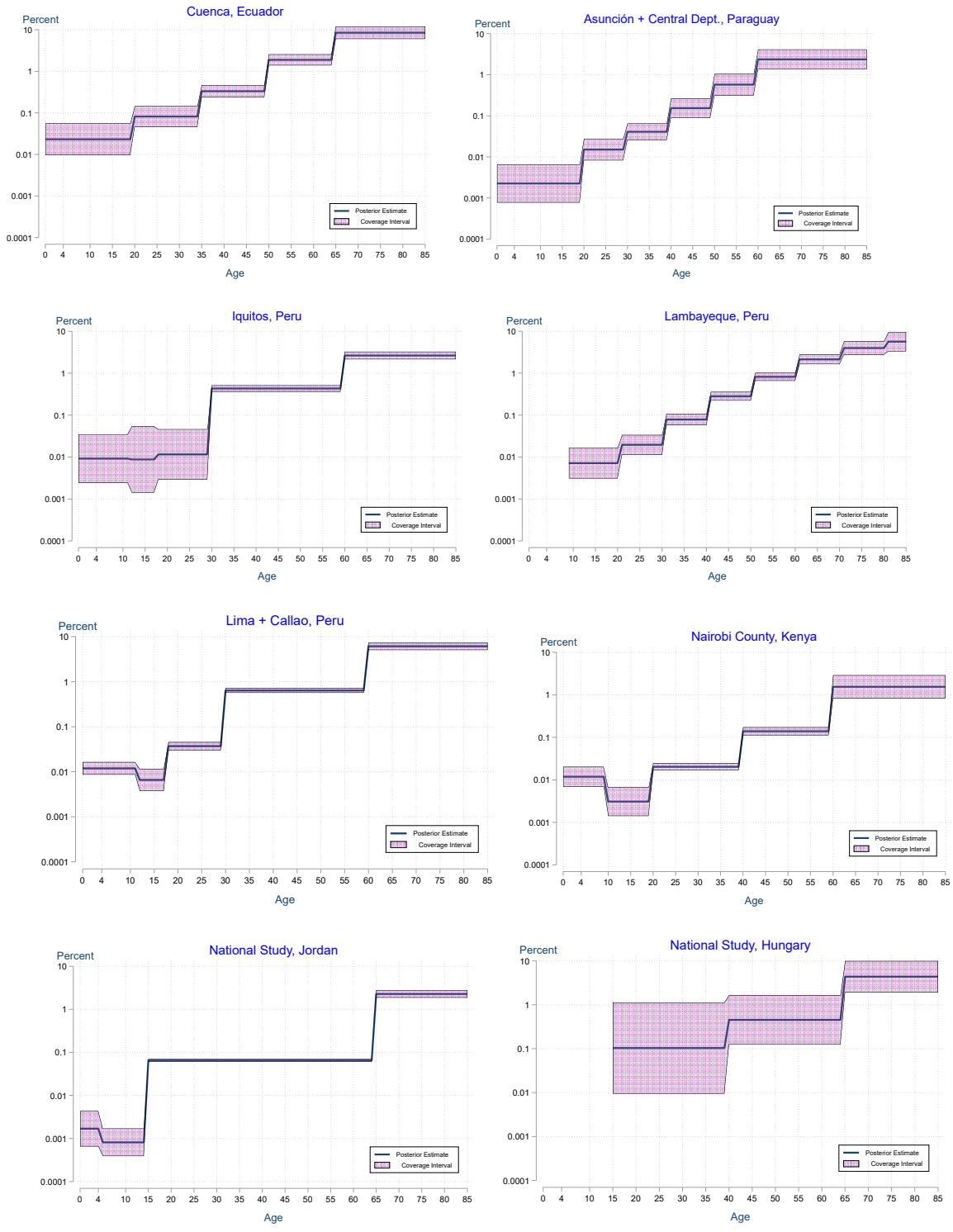

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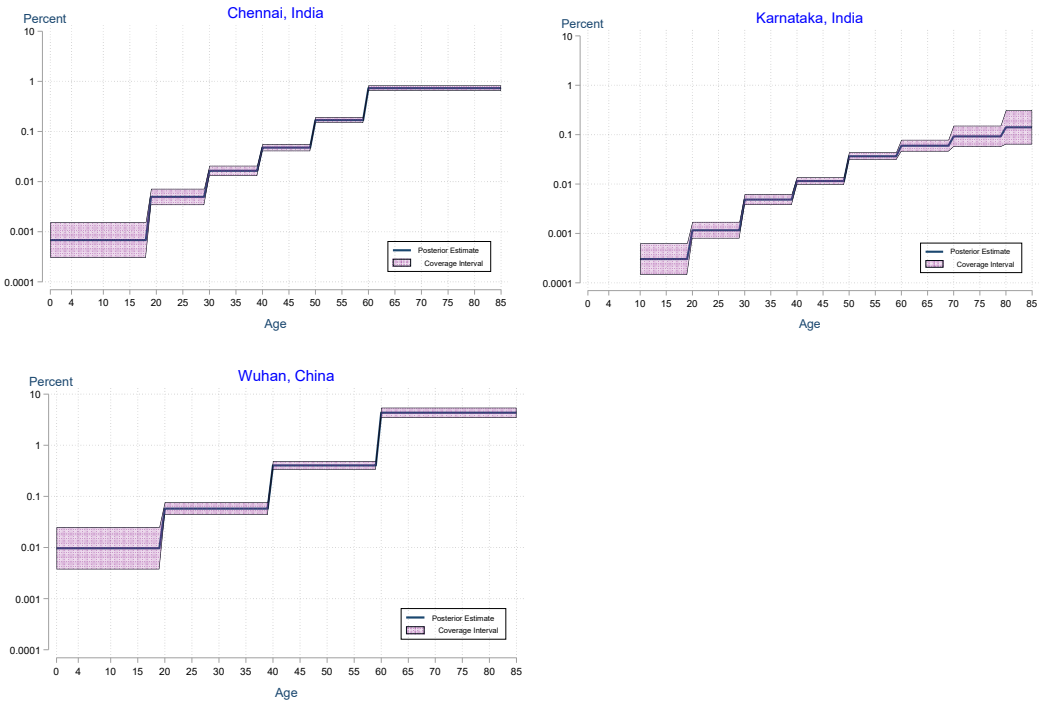


Note: For each location, this figure shows the posterior estimate and 95% credible interval of IFR for each of the age brackets reported in the serology study of that location; each estimate reflects the reported number of COVID-19 fatalities for that age bracket in that location and has not been adjusted for death undercounting.

d. Age-specific IFRs by Age Cohort

Figure A7 – IFR Estimates for Children

Country	Location	Ages	Estimate (95% CI)
India	Karnataka	10–19	0.000 (0.000–0.001)
India	Chennai	0–18	0.001 (0.000–0.001)
Jordan	National Study	5–14	0.001 (0.000–0.002)
Colombia	Barranquilla	11–18	0.001 (0.000–0.004)
Jordan	National Study	0–4	0.002 (0.001–0.004)
Colombia	Barranquilla	5–10	0.002 (0.000–0.006)
Paraguay	Asunción + Central Dept.	0–19	0.002 (0.001–0.005)
Colombia	Cucuta	11–18	0.003 (0.000–0.010)
Colombia	Medellin	11–18	0.003 (0.000–0.008)
Colombia	Cali	11–18	0.003 (0.000–0.008)
Colombia	Bogotá	5–10	0.003 (0.001–0.006)
Colombia	Bogotá	11–18	0.003 (0.001–0.006)
Kenya	Nairobi County	10–19	0.003 (0.001–0.006)
Brazil	Maranhao	10–19	0.003 (0.002–0.005)
Brazil	Maranhao	0–9	0.003 (0.002–0.006)
Colombia	Córdoba	10–19	0.004 (0.001–0.009)
Colombia	Cucuta	5–10	0.004 (0.000–0.016)
Colombia	Villavicencio	11–18	0.004 (0.000–0.016)
Colombia	Bucaramanga	11–18	0.004 (0.000–0.016)
Colombia	Medellin	5–10	0.005 (0.001–0.014)
Chile	3 urban areas	7–14	0.006 (0.002–0.012)
Argentina	Buenos Aires City	0–17	0.006 (0.002–0.013)
Peru	Lima + Callao	12–17	0.007 (0.004–0.011)
Colombia	Cali	5–10	0.007 (0.001–0.018)
Peru	Lambayeque	9–20	0.007 (0.003–0.014)
Colombia	Bucaramanga	5–10	0.007 (0.000–0.027)
Peru	Iquitos	12–17	0.009 (0.000–0.032)
Peru	Iquitos	0–11	0.009 (0.001–0.025)
China	Wuhan	0–19	0.010 (0.003–0.021)
Colombia	Villavicencio	5–10	0.011 (0.000–0.041)
Kenya	Nairobi County	0–9	0.012 (0.007–0.019)
Peru	Lima + Callao	0–11	0.012 (0.009–0.016)
Colombia	Leticia	11–18	0.023 (0.001–0.085)
Ecuador	Cuenca	0–19	0.023 (0.008–0.048)
Colombia	Ipiales	11–18	0.030 (0.001–0.110)
Colombia	Leticia	5–10	0.030 (0.001–0.110)
Colombia	Ipiales	5–10	0.050 (0.001–0.188)

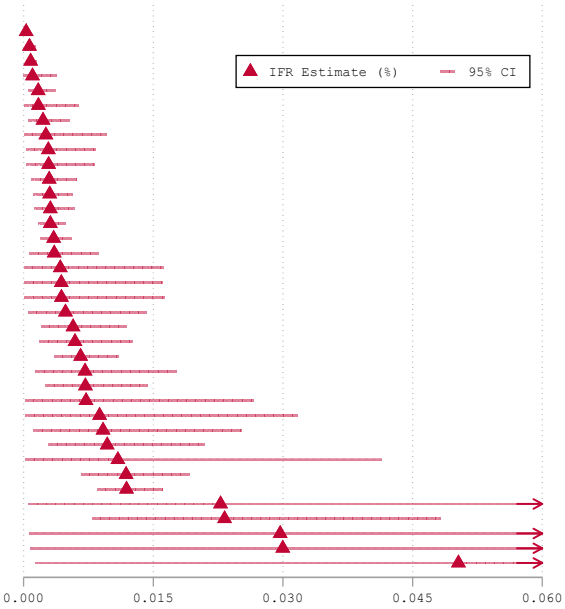


Figure A8 – IFR Estimates for Young Adults

Country	Location	Ages	Estimate (95% CI)
India	Karnataka	20–29	0.001 (0.001–0.002)
India	Karnataka	30–39	0.005 (0.004–0.006)
India	Chennai	19–29	0.005 (0.003–0.007)
Brazil	Maranhao	20–29	0.006 (0.004–0.009)
Peru	Iquitos	18–29	0.012 (0.001–0.033)
Chile	3 urban areas	15–24	0.015 (0.008–0.024)
Paraguay	Asunción + Central Dept.	20–29	0.015 (0.008–0.026)
India	Chennai	30–39	0.016 (0.013–0.020)
Peru	Lambayeque	21–30	0.020 (0.011–0.032)
Kenya	Nairobi County	20–39	0.020 (0.017–0.024)
Brazil	Várzea Grande	20–29	0.021 (0.004–0.053)
Colombia	Leticia	19–40	0.021 (0.003–0.060)
Colombia	Córdoba	20–29	0.026 (0.014–0.042)
Colombia	Villavicencio	19–40	0.028 (0.016–0.043)
Colombia	Medellin	19–40	0.029 (0.022–0.037)
Colombia	Bucaramanga	19–40	0.032 (0.019–0.048)
Brazil	Maranhao	30–39	0.033 (0.026–0.041)
Colombia	Cali	19–40	0.035 (0.027–0.044)
Colombia	Cucuta	19–40	0.037 (0.026–0.050)
Peru	Lima + Callao	18–29	0.037 (0.030–0.045)
Colombia	Bogotá	19–40	0.037 (0.033–0.043)
Paraguay	Asunción + Central Dept.	30–39	0.041 (0.026–0.063)
Brazil	Sao Paulo City	20–34	0.045 (0.036–0.055)
Argentina	Hurlingham	18–30	0.045 (0.009–0.116)
Argentina	Hurlingham	31–40	0.047 (0.005–0.137)
Colombia	Barranquilla	19–40	0.048 (0.038–0.059)
China	Wuhan	20–39	0.058 (0.043–0.075)
Brazil	Cuiabá	20–29	0.058 (0.026–0.106)
Argentina	Buenos Aires City	18–39	0.068 (0.049–0.093)
Colombia	Córdoba	30–39	0.071 (0.047–0.106)
Peru	Lambayeque	31–40	0.079 (0.057–0.105)
Ecuador	Cuenca	20–34	0.082 (0.044–0.136)
Chile	3 urban areas	25–39	0.097 (0.072–0.129)
Hungary	National Study	15–39	0.103 (0.014–0.500)
Colombia	Ipiales	19–40	0.113 (0.054–0.195)

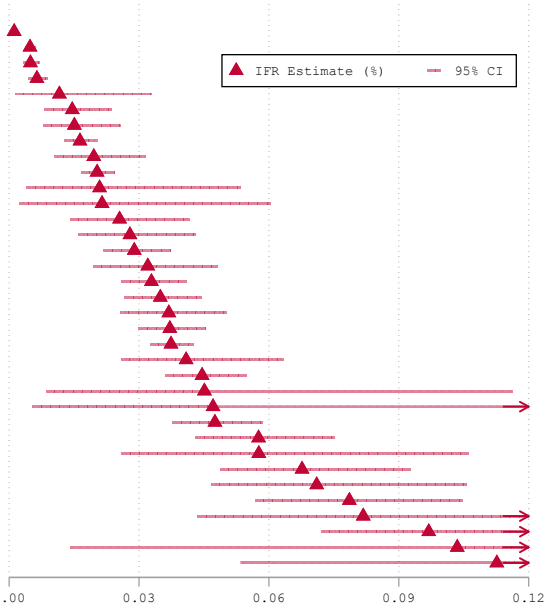


Figure A9 – IFR Estimates for Middle-aged Adults

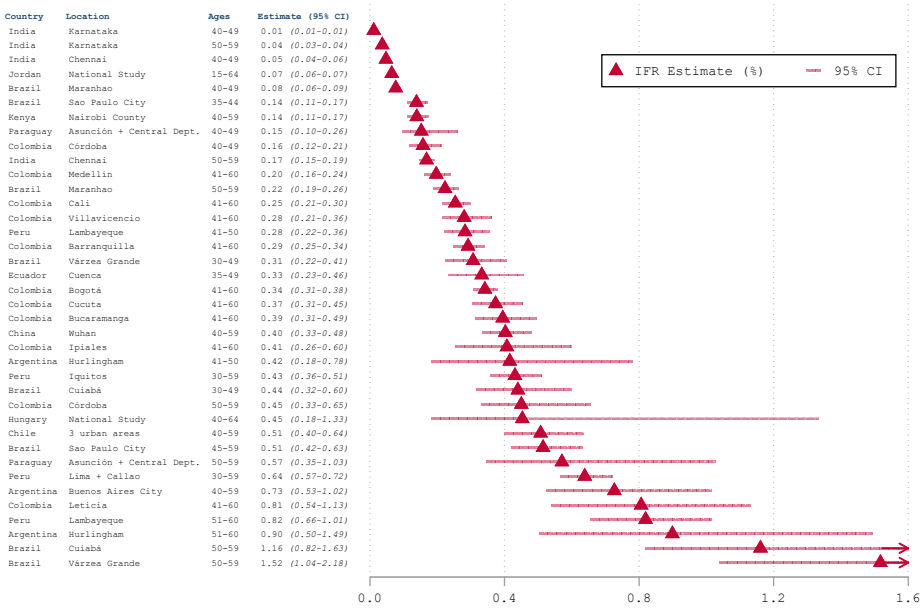
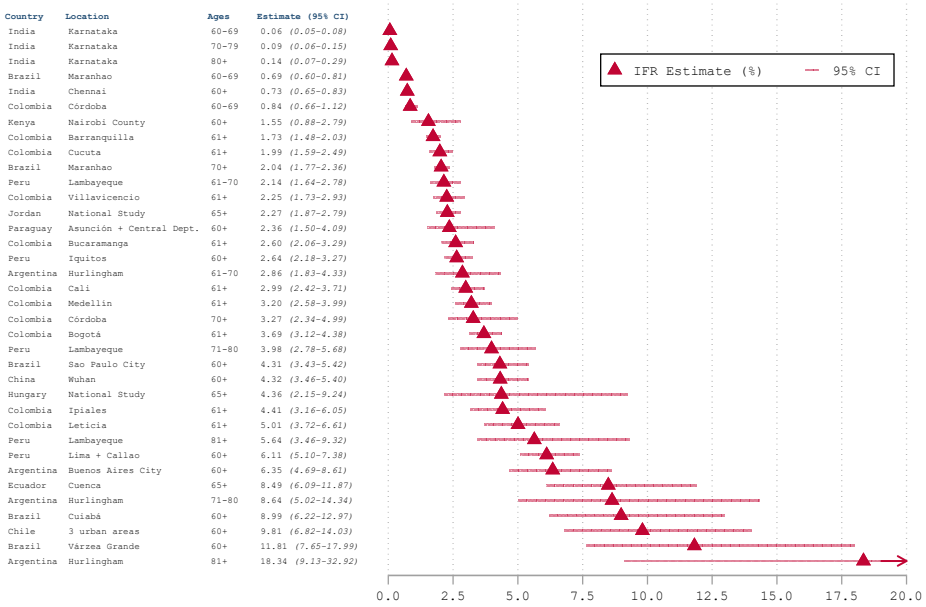


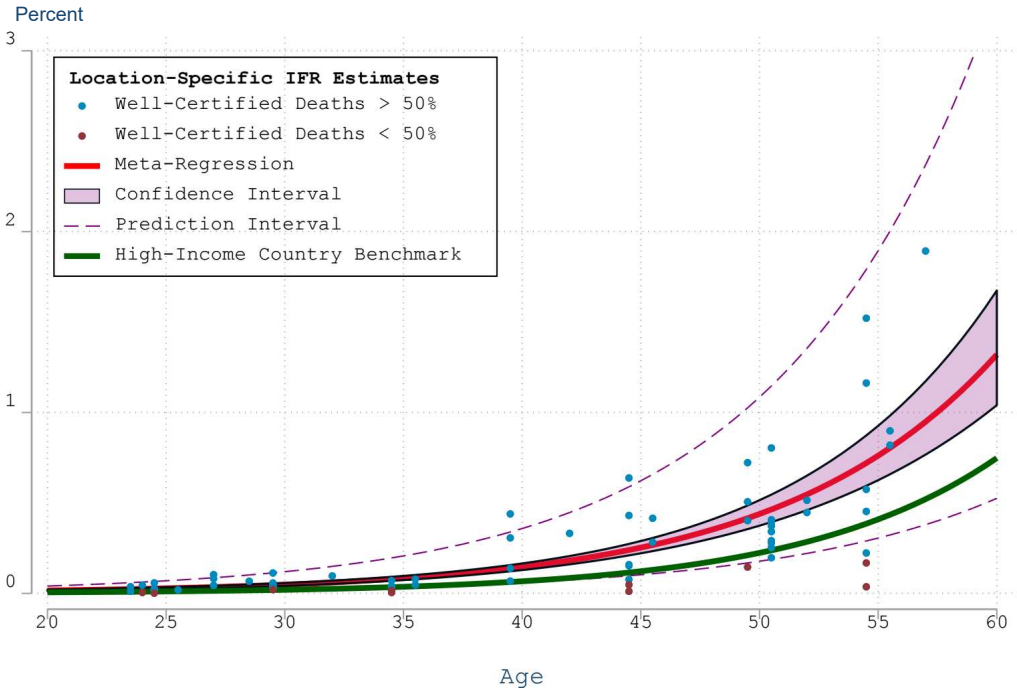
Figure A10 – IFR Estimates for Older Adults



Note: Links to these studies are in the Appendix folder of our GitHub repository.

e. Metaregression Results

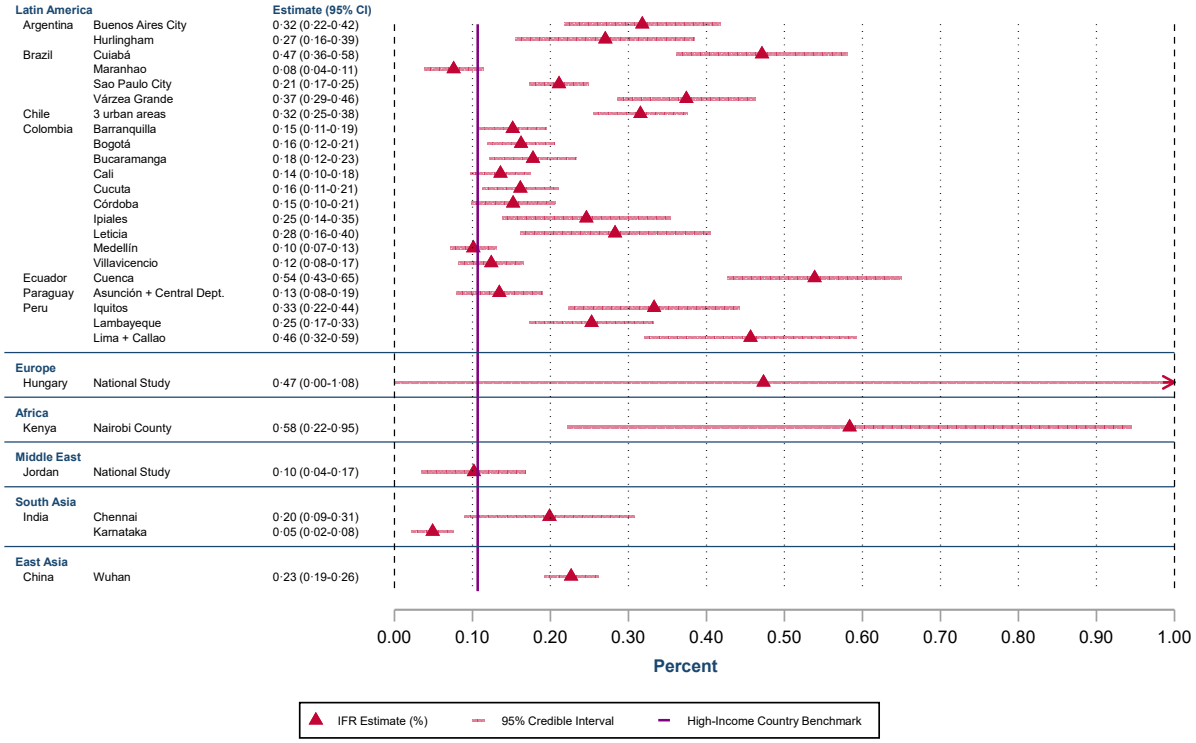
Figure A11 – Age-specific IFR Metaregression in Levels



Note: Links to the studies at each location and categorization by percentage of deaths well-certified are provided in the appendix folder of our GitHub repository.

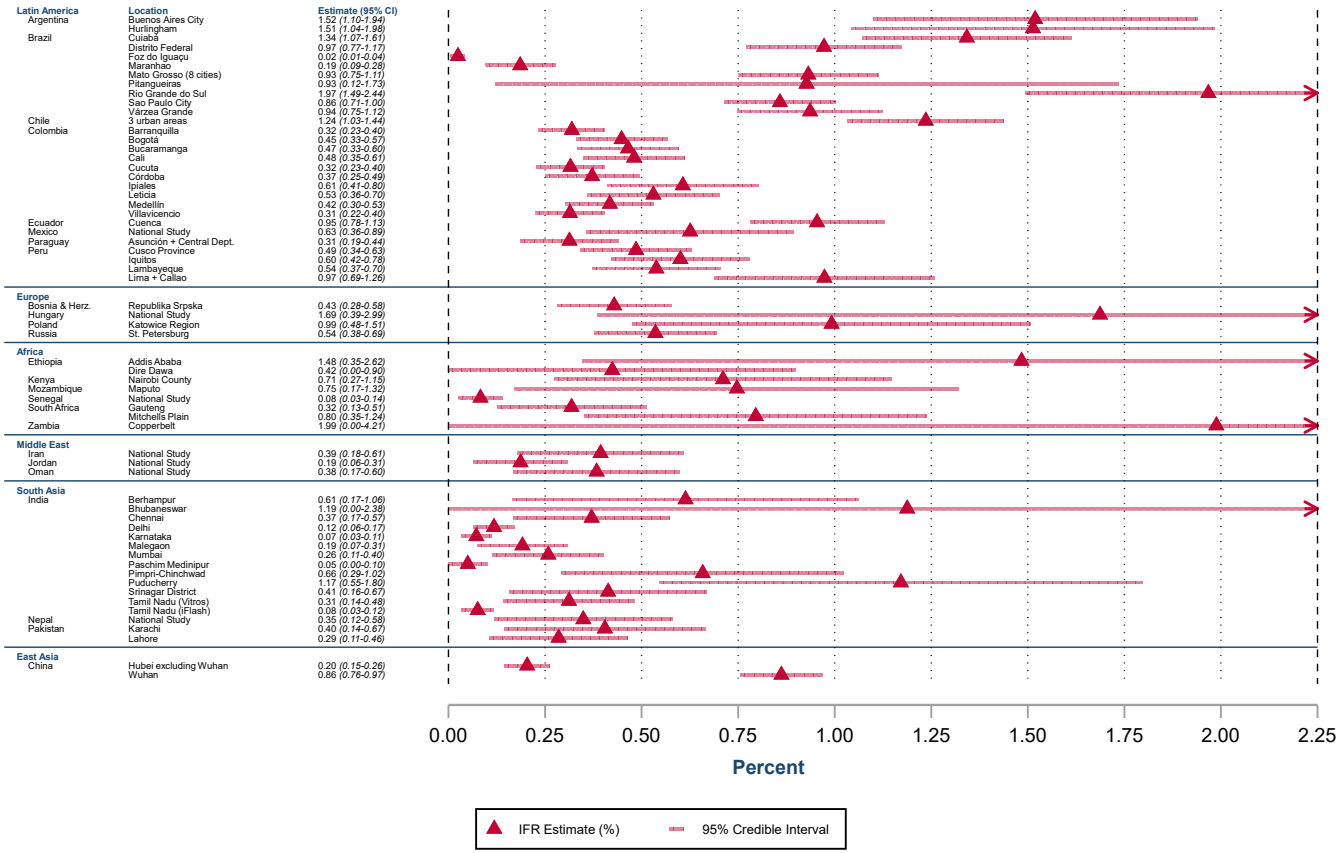
f. Population IFR

Figure A12 – Population IFR (ages 18 to 64)



Note: This figure shows IFR estimates for the population aged 18-64 based on the age structure and age-specific seroprevalence in each location.

Figure A13 – Population IFR (all ages)



g. IFR Estimates from Other Sources

Table A8 compares reported IFRs from studies included in our literature search to our meta-analysis IFR estimates for the corresponding locations, while Table A9 lists reported IFRs from studies identified in our literature search that were excluded from our IFR analysis. It should be noted that IFRs based on reported COVID-19 deaths may be biased due to death undercounting, especially for countries that have a low percentage of well-certified deaths (32).

Table A8 – Comparison of Meta-analysis IFRs to Reported IFRs

Location	IFR stated in the study	Meta-analysis IFR
Brazil: Maranhão*	0.14% (CI: 0.13 - 0.16%) [reported deaths] 0.28% (CI: 0.25 - 0.32%) [excess deaths]	0.13% (CI: 0.12 - 0.14%)
Chile: Coquimbo-La Serena, Greater Santiago, and Talca	1.67% (CI: 1.64 - 1.70%)	1.23% (CI: 1.04 - 1.45%)
Colombia: Córdoba (8 cities)*	0.24% (CI: 0.23 - 0.25%)	0.34% (CI: 0.29 - 0.43%)
Mexico: National	0.47% (CI: 0.44-0.50%)	0.46% (CI: 0.44-0.48%)
Peru: Lambayeque	0.5%	0.49% (CI: 0.43 - 0.56%)
Poland: Katowice region	0.62% (CI: 0.53 - 0.74%)	0.62% (CI: 0.50 - 0.76%)
Russia: St. Petersburg*	0.83% (CI: 0.62 - 1.00%) [excess deaths]	0.54% (CI: 0.41 - 0.73%)
Ethiopia: Addis Ababa #2	≥0.09%	0.20% (CI: 0.09 - 0.63%)
Kenya: Nairobi County*	0.04%	0.06% (CI: 0.05 - 0.07%)
South Africa: Gauteng province	0.28% (CI: 0.27 - 0.30%) [reported deaths] 0.67% (CI: 0.64 - 0.71%) [excess deaths]	0.12% (CI: 0.10 - 0.17%)
South Africa: Mitchells Plain	0.3% (CI: 0.3 - 0.4%) [in-hospital deaths] 0.5% (CI: 0.4 - 0.6%) [excess deaths]	0.31% (CI: 0.27 - 0.37%)
India: national	0.08% (CI: 0.07 - 0.09%) to 0.11% (CI: 0.10 - 0.12%)	0.06% (CI: 0.05 - 0.06%)
India: Chennai*	0.17% (CI: 0.14 - 0.22%)	0.08% (CI: 0.07 - 0.08%)
India: Delhi	0.079% (CI: 0.076 - 0.081%)	0.055% (CI: 0.05 - 0.06%)
India: Kashmir	0.03% (CI: 0.03 - 0.04%)	0.03% (CI: 0.026 - 0.030%)
India: Madurai district*	0.04% (CI: 0.04 - 0.05%)	0.03% (CI: 0.02 - 0.03%)
India: Mumbai (3 wards)*	0.12%	0.08% (CI: 0.08 - 0.09%)
India: Pimpri-Chinchwad	0.17%	0.22% (CI: 0.20 - 0.23%)
India: Puducherry*	0.08%	0.18% (CI: 0.15 - 0.22%)

Note: IFRs are based on reported deaths, not excess deaths, unless otherwise noted. Studies with an asterisk also reported age-specific IFRs. Age-specific IFRs were also reported for Karnataka, India (98).

Table A9 – Reported IFRs for Sero-Only Studies

Location	IFR stated in the study	Type of death	Reason IFR estimate was not generated
Brazil: Rio de Janeiro (multiple regions of the city)	Rio das Pedras: 0.2%; Maré: 0.3%; Rocinha: 0.3%; Cidade de Deus: 0.4%; Realengo: 1.2%; Campo Grande: 1.8%	reported	no death data 4 weeks post-midpoint, insufficient information on assay
South Africa: Jouberton	wave 1: 0.12% (CI: 0.09 – 0.20%) wave 1: 0.16% (CI: 0.13 – 0.23%) wave 2: 0.50% (CI: 0.29 – 1.17%) wave 2: 0.36% (CI: 0.24 – 0.72%)	excess in-hospital excess in-hospital	no death data 4 weeks post-midpoint
South Africa: Klerksdorp, Pietermaritzburg	Klerksdorp: 0.3% (CI: 0.2 – 0.3%) 0.3% (CI: 0.3 – 0.3%) Pietermaritzburg: 0.3% (CI: 0.3 – 0.3%) 0.6% (CI: 0.5 – 0.6%)	in-hospital excess in-hospital excess	no death data 4 weeks post-midpoint
Sudan: Omdurman*	0.64% (CI: 0.62 – 0.75%)	excess	no death data 4 weeks post-midpoint, sampling after February 2021
Iran: Guilan province	0.12%	reported	no death data 4 weeks post-midpoint
Iran: Mazandaran province	0.33%	reported	no death data 4 weeks post-midpoint, no stated start-week and end-week
Palestine	0.11%	reported	no stated start-week and end-week
India: Indore (city, not district)	0.17%	reported	no death data 4 weeks post-midpoint
India: Pune, 5 subwards*	0.21%	reported	no death data 4 weeks post-midpoint
India: Tamil Nadu*	0.05%	reported	Tamil Nadu split into 2 regions based on assay

Note: IFRs are based on reported deaths, not excess deaths, unless otherwise noted. Studies with an asterisk also reported age-specific IFRs.

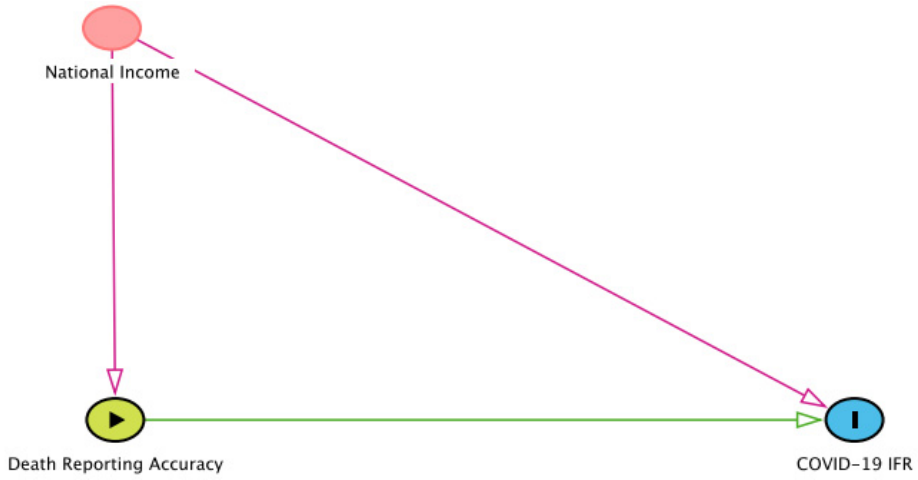
h. Covariates

Table A10 – Correlations Between Covariates, IFR, and Well-Certified Deaths

Covariate	Population IFR	Well-Certified Deaths
Human Development Index	0.63 (0.27-0.83)	0.90 (0.78-0.96)
Log of GDP per capita	0.60 (0.23-0.82)	0.88 (0.73-0.95)
Log(Healthcare Spending)	0.60 (0.22-0.82)	0.93 (0.82-0.97)
Log of GNI per capita	0.60 (0.22-0.82)	0.88 (0.72-0.95)
Hospital Beds Per Capita	0.57 (0.18-0.80)	0.48 (0.06-0.76)
Universal Health Coverage Index	0.55 (0.16-0.79)	0.95 (0.88-0.98)
Skilled Healthcare Workers Per Capita	0.49 (0.08-0.76)	0.69 (0.36-0.86)
Global Health Security Index	0.47 (0.05-0.75)	0.59 (0.21-0.81)
Life Expectancy at Birth	0.43 (0.0-0.73)	0.71 (0.40-0.88)
Healthy Life Expectancy at Age 60	0.40 (-0.04-0.71)	0.83 (0.61-0.93)

This table demonstrates the relationship between various covariates (32), IFR, and the measure of well-certified deaths. This shows that well-certified death is likely to be a primary explanatory variable, which is confounded by relationships with GDP and other national measures when these are used instead. An example of this is shown in the Directed Acyclic Graph below, made using the Daggity online tool: http://www.dagitty.net/dags.html#

Figure A14 – Directed Acyclic Graph of Covariate Relationships



i. Out-of-Sample Analysis

Our analysis excludes seroprevalence estimates that geographically overlap with an already included location, as discussed in supplementary appendix section 1.b. The body of the paper also excludes IFR estimates that overlap with an included IFR, though we still calculated population-wide IFRs for these out-of-sample locations. The table below lists these IFR estimates:

Table A11 – IFRs for Out-of-Sample Locations with Geographical Overlap

Location	Excluded from body of paper	Meta-analysis IFR
Brazil: São Paulo*	No	0.84% (CI: 0.76 - 0.93%)
Brazil: São Paulo #2*	Yes	0.77% (CI: 0.66 - 0.88%)
Ethiopia: Addis Ababa*	No	0.11% (CI: 0.07 - 0.16%)
Ethiopia: Addis Ababa #2	Yes	0.20% (CI: 0.09 - 0.63%)
Ethiopia: Addis Ababa #3*	Yes	0.002% (CI: 0.001 - 0.005%)
India: national*	Yes	0.06% (CI: 0.05 - 0.06%)
India: Kashmir (Srinagar district)*	No	0.06% (CI: 0.06 - 0.07%)
India: Kashmir*	Yes	0.03% (CI: 0.026 - 0.030%)
India: Tamil Nadu (Vitros districts)	No	0.07% (CI: 0.06 - 0.07%)
India: Madurai district (in Tamil Nadu)*	Yes	0.03% (CI: 0.02 - 0.03%)
China: Wuhan*	No	0.86% (CI: 0.76 - 0.97%)
China: Wuhan #2*	Yes	0.71% (CI: 0.59 - 1.06%)

*age-specific seroprevalence also reported in the paper

IFRs from studies of the same location may differ by sampling time due to factors such as improved treatment or new SARS-CoV-2 variants. Despite this, population-wide IFRs were relatively similar for studies that sampled the same location, as illustrated in the table above. These consilient results increase confidence that methodological differences between studies likely do not strongly bias our IFR estimates, in contrast to the order of magnitude difference in IFR between locations stratified by percentage of well-certified deaths, as shown in the body of the paper. Addis Ababa #3 remains the only outlier, possibly due to lower test specificity resulting from cross-reactivity (see supplementary appendix section 2.a), low sample size in comparison to the other two Addis Ababa studies, or sampling in late April 2020 when under-estimation of COVID-19 deaths may have been greater than the July/August 2020 time period during which the other two studies sampled.

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