Rapid Reviews COVID-19

Review 1: "The infection fatality rate of COVID-19 inferred from seroprevalence data"

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RR:C19 Evidence Scale rating by reviewer:

- **Potentially informative.** The main claims made are not strongly justified by the methods and data, but may yield some insight. The results and conclusions of the study may resemble those from the hypothetical ideal study, but there is substantial room for doubt. Decision-makers should consider this evidence only with a thorough understanding of its weaknesses, alongside other evidence and theory. Decision-makers should not consider this actionable, unless the weaknesses are clearly understood and there is other theory and evidence to further support it.

Review:

The concept of estimating the Infection Fatality Ratio (IFR) by dividing reported deaths by an estimated of those ever infected through a seroprevalence estimate is, in principle, a good one. The IFR is an important concept and it is very difficult to estimate. The paper does a good service in collating available data and offering the computations. Many of the limitations are noted, and I agree with these. However, the limitation are so important that I do not believe that substantial conclusions can (yet) be drawn from this analysis. I do not believe that the evidence presented here supports such a strong statement as "... the fact that its IFR is typically more lower than originally feared". I do believe that these data are useful and add to the emerging picture on IFR and that a continued collation of data will contribute to more firm conclusions being drawn.

The main limitations that I note are as follows:

1. Is it recognised that the IFR varies very substantially by age. This (i) makes an average IFR not very meaningful per se, (ii) means that differences in the age-composition of populations and the pattern of spread of the epidemic substantially confound the analysis (to such an extent that it is not overcome by the basic <70 vs >70 years old split presented). This also means that summaries (e.g. the the median across a range of countries included in the analysis) potentially over-simplifies things.
2. There is little accounting for the variable quality of the data that go into the

estimates. That is, some studies will be of very high quality and give a high likelihood of a good estimate of IFR, but others will not (due to factors like non-representative samples in the serosurvey or variable methods for counting deaths that can be attributed to COVID-19). It would be useful to show how indicators of quality (decided a priori) relate the resulting IFR estimate. Related to this point, it is interesting that estimates of IFR are higher in settings with higher death counts overall. This could be a real effect (less care available due to overburdened hospitals, or more infections among older people) but it could also be the result of a bias (e.g. countries with have more complete death reporting have commissioned more representative serosurveys). Without further information it is difficult to tease these apart.

3. The inclusion of data from blood donors does - as the author notes - potentially introduce the health-volunteer effect by which a lower prevalence of infection is measured in the sample, thereby increasing the apparent IFR.

4. The method for adjusting for the performance characteristics of the tests used is not well explained or justified. It seems to me that substantial uncertainty is introduced by this and it ought to be communicated in the analysis. Similarly, the correspondence of the cumulative deaths reported and the period of the survey is not always perfect or perfectly known but uncertainty within this may be important and this should also be reflected in the estimates of IFR.

5. The completeness of the reporting is not fully assured. I note that the reports used are drawn from a search of "PubMed (LitCOVID), medRxiv, bioRxiv, and Research Square". Could this miss "grey literature", official government reports etc (which may be among the most reliable reports)?