Rapid Reviews COVID-19

Review 1: "Age-Specific Mortality and Immunity Patterns of SARS-CoV-2 Infection in 45 Countries"

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RR:C19 Evidence Scale rating by reviewer:

- **Strong.** The main study claims are very well-justified by the data and analytic methods used. There is little room for doubt that the study produced has very similar results and conclusions as compared with the hypothetical ideal study. The study's main claims should be considered conclusive and actionable without reservation.

Review:

This is a very interesting paper dealing with the topic of using a "hard outcome" (COVID-19 deaths) to compare COVID-19 burden between countries and infer the true number of infections. The authors note that apart from differences in the age distribution and co-morbidities in the population of each country, an additional complication that needs to be taken into account is that, in some countries, COVID-19 mortality is heavily influenced by large outbreaks in nursing homes/LTHCF for the elderly. Thus, they combine seroprevalence data from 12 countries/areas and COVID-19 death data from 45 countries to estimate age-specific infection fatality ratios. They use mortality data for individuals >65 years old from England as for this country they had the necessary information to separate out deaths in nursing homes from other deaths. They find consistent patterns of death in individuals <65 years old but highly heterogeneous relative risk of death for >65 between countries and suggest that death data in younger individuals can provide a robust indicator of the proportion of the population infected.

Some comments:

1. As the authors mention, estimates of the IFR should be derived from studies that carefully estimate the number of infected individuals in a particular setting. The 18 seroprevalence studies from 15 countries/regions were quite heterogeneous (surveys among blood donors, hospital outpatients and general population – for the latter, it is not clear how sampling was performed). Some discussion on this would be helpful, in particular as it is mentioned in the supplementary material that the results of these surveys were representative of the general population.

2. The authors performed the analysis assuming a baseline relative infection attack rate of 0.7 for individuals aged ≥ 65 , relative to those <65, and equal infection attack rates across age groups <65 years. This is based on the argument that older

individuals have fewer social contacts and are more likely to be isolated through shielding programmes. Two things to consider here: (a) Children seem to have a lower susceptibility to infection as compared to 19+ or 60+ (eg. Zhang et al, Science 2020, Jing et al, Lancet Inf Dis 2020, Li et al, Clin Inf Dis 2020). (b) Schools closed early in the epidemic in many countries, so children 0-18 yrs reduced their social contacts as well. What happens if a lower relative infection rate is assumed for children compared to adults?

3. The authors should mention in the introduction that the number of observed deaths has been used to calculate backwards the number of infections and refer to the relevant papers (e.g. Flaxman et al, Nature 2020 with estimates for 11 countries).

4. It would be good to mention as well that apart from differences in the age distribution and co-morbidities, there are large differences in the number of nursing and elderly home beds across countries (e.g. Nordic countries vs countries in South Europe).

5. The authors mention that they have used death data for those aged >65 years old only from England as "granularity of the data allows us to remove deaths in nursing home populations". However, in Figure 1C, they compare the reconstructed number of deaths with reported data for age-groups 65+ for a subset of countries where nursing home deaths could be excluded. It is not clear then why only data from England were used for the 65+ age group.