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## COVID-19 and inter-generational solidarity

The Editors<sup>1</sup> rightly draw attention to the catastrophic effects that the COVID-19 pandemic continues to have on children and younger people. This concern is entirely justifiable, as is the Editorial's call for young people to have more voice in decision making. The Editorial observes that younger people are under-represented in political leadership, implying that this contributes to their disproportionate vulnerability to the effects of COVID-19.

The Editors also imply that older people are over-represented and consequently benefit from favourable policies; indeed, they urge older adults to "let go of established power structures".<sup>1</sup> Yet, even in evidently gerontocratic countries, health policies actively discriminate against older people. In India, for example, where the average age of national members of parliament is 57.5 years, third doses of COVID-19 vaccines are being rolled out to front-line workers and will soon be available to anyone aged 15 years or older. Yet, by early January, 2022, millions of people 60 years or older were yet to receive a second or even first dose.<sup>2</sup> Rather than between the interests of people at younger and older ages, COVID-19 responses are more subject to trade-offs between economic interests and the health of entire populations.<sup>3</sup>

It is essential to avoid simple assumptions based on age stereotypes and to foster a shared community of interest between children, older people, and everyone aged in between.

I declare no competing interests.

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- 1 The Lancet. Children and adolescents deserve a better future. *Lancet* 2022; **399**: 117.
- 2 Ghosh S, Guntupalli A, Lloyd-Sherlock P. India's vaccine policy has left those most at risk exposed to the third wave of Covid-19. Jan 6, 2022. <https://scroll.in/article/1014319/indias-vaccine-policy-has-left-those-most-at-risk-exposed-to-the-third-wave> (accessed Feb 24, 2022).
- 3 Lloyd-Sherlock P. Time to rethink generational justice. *Lancet* 2021; **397**: 21–22.

## Allocated but not treated: the silent 16%

The RECOVERY Collaborative Group has provided timely, robust evidence for managing hospitalised patients with COVID-19, including their randomised controlled trial supporting the use of tocilizumab.<sup>1</sup> However, results from other smaller randomised controlled trials of tocilizumab (and sarilumab), particularly those with a placebo control group, did not show a mortality benefit of interleukin-6 inhibition versus control. In seeking to understand the totality of the data, results of any meta-analysis will be heavily weighted by RECOVERY trials, the largest population studied. A complete and nuanced understanding of the trial results is thus crucial for accurate interpretation.

Although an intention-to-treat analysis is important to preserve the prognostic balance that is reached through randomisation, in the open-label RECOVERY trial, one in six (317 [16%] of 1964) allocated patients did not receive tocilizumab. A further 3% were missing data on whether or not they received tocilizumab. The authors wrote that "the size of the effects of tocilizumab reported in this paper are therefore an underestimate of the true effects", an assertion that was echoed in Shruti Gupta and David E Leaf's Comment.<sup>2</sup> This interpretation assumes that people who were allocated to but not treated with tocilizumab were as or more likely to die than those who received the drug and, furthermore, that there is no possible harm from treatment. However, if mortality in the 16% of patients who did not receive tocilizumab was lower than in the control group or the patients who were treated with tocilizumab, then the result could be biased away from the null. Fortunately, given that the data exist, we do not need to pursue the academic exercise of debating bias towards or away from the null. We respectfully request the authors to contrast the demographics, baseline clinical status, and outcomes of

patients allocated to but not treated with tocilizumab with those who did receive treatment.

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- 1 RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397**: 1637–45.
- 2 Gupta S, Leaf DE. Tocilizumab in COVID-19: some clarity amid controversy. *Lancet* 2021; **397**: 1599–601.

## Authors' reply

Randomised controlled trials generally seek to estimate the effect of assignment to an intervention (ie, the intention-to-treat effect) rather than the effect of adhering to an intervention (ie, the per-protocol effect). Intention-to-treat analysis is the only type of analysis to guarantee that the patient groups being compared remain balanced with respect to their baseline characteristics (differing only due to chance), thus allowing valid randomised comparisons of these groups.<sup>1</sup> Of course, in any trial, some patients assigned to an intervention might not receive it (ie, drop out), whereas others who are not assigned to the intervention might subsequently receive the intervention (ie, drop in). Because both of these effects reduce the difference between randomised groups in exposure to the randomised intervention, intention-to-treat analyses tend to underestimate the effect of full adherence.<sup>2</sup> Although it can be tempting in such circumstances to try to estimate the effect of



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