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- 1 Perico N, Cortinovis M, Suter F, Remuzzi G. Home as the new frontier for the treatment of COVID-19: the case for anti-inflammatory agents. *Lancet Infect Dis* 2022; published online Aug 25. [https://doi.org/10.1016/S1473-3099\(22\)00433-9](https://doi.org/10.1016/S1473-3099(22)00433-9).
- 2 Little P, Stuart B, Andreou P, et al. Primary care randomised controlled trial of a tailored interactive website for the self-management of respiratory infections (Internet Doctor). *BMJ Open* 2016; **6**: e009769.
- 3 Ravichandran R, Mohan SK, Sukumaran SK, et al. An open label randomized clinical trial of indomethacin for mild and moderate hospitalised Covid-19 patients. *Sci Rep* 2022; **12**: 6413.
- 4 Gordon DE, Hiatt J, Bouhaddou M, et al. Comparative hostcoronavirus protein interaction networks reveal pan-viral disease mechanisms. *Science* 2020; **370**: eabe9403.
- 5 Suter F, Consolaro E, Pedroni S, et al. A simple, home-therapy algorithm to prevent hospitalisation for COVID-19 patients: a retrospective observational matched-cohort study. *EClinicalMedicine* 2021; **37**: 100941.

Authors' reply

We appreciate the comments on our Review article¹ from Alberto Donzelli. We agree that inflammation plays an initial and defensive role in fighting infection. The question is how you define "initial". When symptoms manifest, inflammation might already be there, possibly for a few days. Our objective is to inhibit the hyperinflammation that invariably follows and is responsible for functional impairment in the lung and other organs.

Donzelli refers to a randomised controlled trial showing that the use of ibuprofen is unsafe and has unfavourable outcomes in respiratory infections; however, the study in question was published in 2016, well before the COVID-19 pandemic, and was designed to assess the effectiveness of an internet-delivered intervention.

With regard to indometacin, Donzelli refers to a randomised controlled trial involving patients admitted to hospital, a different setting from ours; moreover, at the time when our studies were designed, this information was simply not available.

Concerning nimesulide and celecoxib, which are recommended in the absence of any successful randomised

controlled trials, it is important to bear in mind that we need data in order to create the theoretical basis for a randomised controlled trial, and this is exactly what we have done with our two previous studies.^{2,3}

Indeed, we agree with Donzelli that the results of secondary outcome analyses should never be considered conclusive, but instead as hypothesis generating. This is why, based on results from secondary outcome analyses in our first matched-cohort study,¹ we designed our second matched-cohort trial³—which Donzelli overlooked—to compare the incidence of hospital admission (considered the primary and single endpoint) in patients treated by their family doctors with the proposed algorithm versus controls treated according to other therapeutic schedules. This controlled study showed that there was a statistically significant reduction in the single primary endpoint in patients treated according to the standardised algorithm. The statistical significance of this single endpoint was independent of any Bonferroni adjustment for multiple comparisons, regardless of the number of patients involved and of the non-randomised design. We are planning a randomised controlled trial (ClinicalTrials.gov, NCT05413642) to further corroborate the robustness of this finding. However, planning and finalising randomised controlled trials takes years and requires a huge amount of resources, so randomised controlled trials are not necessarily the most efficient research approach to solving problems in the context of urgent public health decision making.⁴

The response to this issue by Derek Angus⁵ is even more direct and straightforward: "If a physician agrees that evidence is uncertain, that the chance of benefit outweighs chance of harm, then just do it. The consequences for the patient are salient and immediate, in contrast to the benefit throughout participation in an RCT."

We declare no competing interests.

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- 1 Perico N, Cortinovis M, Suter F, Remuzzi G. Home as the new frontiers for the treatment of COVID-19: the case for anti-inflammatory agents. *Lancet Infect Dis* 2022; published online Aug 25. [https://doi.org/10.1016/S1473-3099\(22\)00433-9](https://doi.org/10.1016/S1473-3099(22)00433-9).
- 2 Suter F, Consolaro E, Pedroni S, et al. A simple, home-therapy algorithm to prevent hospitalisation for COVID-19 patients: a retrospective observational matched-cohort study. *EClinicalMedicine* 2021; **37**: 100941.
- 3 Consolaro E, Suter F, Rubis N, et al. A home-treatment algorithm based on anti-inflammatory drugs to prevent hospitalization of patients with early COVID-19: a matched-cohort study (COVER 2). *Front Med* 2022 **9**: 785785.
- 4 Frieden TR. Evidence for health decision making — beyond randomized, controlled trials. *N Engl J Med* 2017; **377**: 465–75.
- 5 Angus DC. Optimizing the trade-off between learning and doing in a pandemic. *JAMA* 2020; **323**: 1895–96.

Monkeypox in pregnancy: update on current outbreak

The monkeypox case count in the current global outbreak surpassed 52 000 on Sept 1, 2022. Community transmission is affecting people considered to be at high risk of severe disease, including pregnant women and neonates, albeit in small numbers so far. As of Sept 2, 2022, ten cases of monkeypox in pregnant women have been reported worldwide, mostly via local news media rather than medical or public health publications, with the first case reported in the USA on July 23, 2022.¹ Based on available information, vertical transmission did not occur; the neonate received prophylactic vaccinia immunoglobulin and did not develop monkeypox disease.

On Aug 4, 2022, the Government of São Paulo, Brazil, announced that two pregnant women had been diagnosed with monkeypox and



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For monkeypox case count see

<https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html>