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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 hyper-inflammation 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 indomethacin, 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,4 we designed our second matched-cohort trial—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.”6

We declare no competing interests.

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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...
were being monitored by healthcare professionals. By Aug 26, the Brazilian health authorities had reported a total of nine cases in pregnancy (four in São Paulo, three in Rio de Janeiro, one in Minas Gerais, and one in Ceará). Eight had monkeypox PCR-confirmed by Sept 1, whereas the woman in Ceará had monkeypox PCR-confirmed by Aug 14. She was admitted to hospital with skin lesions on Aug 4 and gave birth to a healthy infant on Aug 14. She was isolated from her baby after birth and discharged healthy on Aug 17. There was no vertical transmission; the neonate was asymptomatic but remained in hospital when the mother was discharged.

Reassuringly, it appears that, so far, none of the monkeypox infections reported in pregnant women have been severe, and there has been no evidence that pregnant women have more severe disease or worse outcomes than non-pregnant people. There is, however, an urgent need for an international registry or reporting system to better understand the course, management, treatment, and outcomes of monkeypox, as well as the safety and effectiveness of vaccination, in populations at high risk, including the mother–fetus dyad, so that patients worldwide can be provided with accurate advice and evidence-based care. Unfortunately, we are currently having to rely on news outlets providing sparse information that is not externally verifiable. Nevertheless, a higher number of monkeypox infections in pregnancy have now been reported in non-endemic versus endemic countries, highlighting decades of neglect by international communities of such infectious diseases in endemic countries. If there are lessons to be learnt in the current monkeypox outbreak, we are failing to learn them.

AK and PO’B are members of the Royal College of Obstetricians and Gynaecologists’ group developing guidance on monkeypox in pregnancy. PO’B is Vice-President of the Royal College of Obstetricians and Gynaecologists. All other authors declare no competing interests.

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Further humoral immunity evasion of emerging SARS-CoV-2 BA.4 and BA.5 subvariants

SARS-CoV-2 BA.4 and BA.5 lineages have been the dominant strains in most regions worldwide and are continuously gaining mutations in the receptor-binding domain. Multiple BA.4 and BA.5 subvariants with Arg346 mutations in the spike glycoprotein have been identified in various countries, such as BA.4.6, BA.7, BA.5.2.6, BA.4.1.9, and BE.1.2 harbouring Arg346Thr; BA.4.7 and BF.13 harbouring Arg346Ser; and BA.5.9 with Arg346le mutations (appendix p 4). These subvariants, especially BA.4.6, exhibit growth advantages compared with other variants including the original BA.4 and BA.5 strains. Previous studies have identified Arg346 as an important immunogenic residue because Arg346 mutations would allow the virus to escape neutralisation by a large group of neutralising antibodies. Unlike Arg346Lys carried by BA.1.1, which maintained a similar chemical property, mutations from Arg to either Thr, Ser, or Ile correspond to a much stronger shift in antibody recognition. The efficacy of vaccines and neutralising antibody drugs against these BA.4 and BA.5 sublineages needs immediate evaluation.

In this study, we measured the neutralising titres of plasma samples against the SARS-CoV-2 BA.4 and BA.5 subvariants with Arg346 mutations. The plasma samples were obtained from vaccinated

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See Online for appendix