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1 **Letter of reply to Lancet 14-4111**

2
3 Sir

4
5 Del Mar et al. assert that their recent Cochrane review was based on full clinical study
6 reports of all manufacturer-sponsored randomized trials. In fact, only a subset (46 of the 107
7 Clinical Study Reports obtained) were formally analysed.¹ The study undertaken by Muthuri
8 et al. was indeed funded by Roche, but its design, conduct, interpretation and manuscript
9 preparation were conducted independently of the funder.² Exhaustive attempts were made
10 to obtain datasets suitable for analysis from around the world. Compared with the 80
11 datasets received, relatively few (n=15) were not shared due to review board or
12 governmental restrictions (n=3) or inability to meet project timelines (n=12).² None of the
13 contributors of data declared industry funding for the acquisition or assembly of their dataset.

14
15 We do not dismiss the findings in the Cochrane review. Indeed, the finding that there was no
16 signal suggesting that neuraminidase inhibitors (NIs) reduced serious complications¹ is not
17 unexpected given that the clinical trials reviewed were conducted in community settings,
18 were based on mostly healthy patients suffering from mild influenza-like illness, and were not
19 designed or powered to assess impact on severe illness. Indeed, their assessment of
20 effectiveness of oseltamivir against hospital admission was based on 4 394 adults and 1 359
21 children; pneumonia – 4 452 subjects; and serious complications – 3 675. Mortality, a
22 hallmark of pandemics and seasonal outbreaks, could not be assessed due to the absence
23 of deaths in the oseltamivir trials. The same limitations apply to the pooled analysis of 3 564
24 subjects in 10 RCTs of oseltamivir treatment by Kaiser et al,³ which unlike the Cochrane
25 review, showed that treatment was associated with reductions in influenza-related lower
26 respiratory complications and hospitalisation from any cause.

27
28 In contrast, the observational data assembled and analysed by Muthuri et al. used individual
29 participant data (an approach not pursued in the Cochrane review) and focused on patients
30 hospitalised with severe pandemic influenza A/H1N1 2009 infection (86% laboratory
31 confirmed).² Many patients had risk-factors for severe illness; the dataset was extremely
32 large (n=29 234), and compared with no treatment, NI treatment was associated with a
33 reduction in mortality risk.

34
35 While we agree with Del Mar et al that randomised trials are less prone to error from bias
36 than observational studies,⁴ we do not accept that meta-analysis of existing RCTs,
37 conducted in community patients with “relatively benign influenza”,¹ and which suffer
38 “problems in the design of many of the studies that were included”,¹ can resolve pressing
39 questions about the role of NIs in the treatment or prevention of life-threatening influenza.

40
41 Thus, we reassert that the findings of the Cochrane Collaboration¹ do not conflict with those
42 of the recent large observational study by Muthuri et al;² rather, both studies reveal
43 beneficial effects of NIs in completely different scenarios (settings, severity, comorbidity and
44 background immunity).

45
46 Public outcry would indeed be justified if pandemic planners relied only on the available
47 RCTs when making decisions about how to prevent and treat severe influenza.

48
49
50 Jonathan S. Nguyen-Van-Tam
51 Peter J.M. Openshaw
52 Karl G. Nicholson

53
54 Conflicts of interest: unchanged since original Commentary was written

55

56 **References**

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