time measurement were similar to those for logins and page views. However, we agree with the authors that the finding that overall use of the website seemed greater by people with high compared with low socioeconomic status suggests that these crude indices of use did not mediate the effectiveness of StopAdvisor for smokers of low socioeconomic status. We are keen to investigate more nuanced measures of engagement in future research.

The third issue relates to what is described as a so-called borderline result and the clinical significance of the effect size. Within classical inferential statistics, the result cannot be borderline—the results is either significant or not, and in this case it was significant. With respect to the effect size, we strongly disagree with the authors about its clinical significance. As described in our discussion, modest (and even small) effect sizes can be of great clinical significance because of the huge health gains associated with stopping smoking: effects as little as 1% on the proportion of people with 6 month sustained abstinence would result in at least 3 additional years of life for every 100 smokers aged 40 years given an intervention.[6] We also discussed how the effect size for smokers with low socioeconomic status was similar to other modes of delivery for behavioural support.

With respect to the fourth issue of possible duplicate users, an email address could only be used once on our website and was secured to the treatment allocation. Additionally, our eligibility criteria included the provision of valid telephone numbers and postal addresses for follow-up. We screened these personal details to ensure they were unique before participants were included in the trial, which resulted in the exclusion of 19 people (see figure 1 in the Article[1]).

Finally, Haldar and Kant raise issues with our reporting of the analysis of the saliva samples. In fact, we did report the number of participants who did not provide verified saliva samples as a footnote to table 2 (207 [4·5%] of all 4613 participants for the primary outcome and 392 [8·5%] of 4613 for the secondary outcome, with similar numbers between intervention groups in each socioeconomic status subsample). Although we did not report descriptive statistics for the analysis of saliva samples, we did describe in detail the decision procedure for judgment of whether a saliva sample provided verification of the reported abstinence from smoking. Additionally, we do not see how our analysis of the saliva samples could have accounted for the pattern of results obtained.

All authors report receiving grants from National Prevention Research Initiative during the study; JB reports grants from Pfizer, outside of the submitted work. RW reports receiving grants and personal fees from companies that develop and manufacture smoking cessation drugs, outside of the submitted work, and has had a patent issued for the "Nicotine Cannon" (novel nicotine delivery device).

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1 Brown J, Michie S, Geraghty AWA, et al. Internet-based intervention for smoking cessation (StopAdvisor) in people with low and high socioeconomic status: a randomised controlled trial. *Lancet Respir Med* 2014; **2:** 997–1006.
2 Graham AL, Papandonatos GD. Reliability of internet- versus telephone-administered questionnaires in a diverse sample of smokers. *J Med Internet Res* 2008; **10:** e8.
3 Graham AL, Papandonatos GD, Bock BC, et al. Internet- vs telephone-administered questionnaires in a randomized trial of smoking cessation. *Nicotine Tob Res* 2006; **8** (suppl 1)**:** S49–57.
4 Office for National Statistics. The National Statistics socio-economic classification user manual. Basingstoke: Palgrave Macmillan, 2005.
5 Shortreed SM, Bogart A, McClure JB. Using multiple imputations to accommodate time-outs in online interventions. *J Med Internet Res* 2013; **15:** e252.
6 West R. The clinical significance of 'small' effects of smoking cessation treatments. *Addiction* 2007; **102:** 506–09.

Neuraminidase inhibitors for influenza: fully evaluating benefits and harms

Neuraminidase inhibitors are the only drugs for treating influenza at present that the virus does not rapidly evolve resistance against. The debate is ongoing about whether the benefits outweigh the harms (or costs) of neuraminidase inhibitors, with evidence[1-4] supporting both sides. The present debate mostly focuses on the strength of benefits from the direct effects of neuraminidase inhibitors relative to the potential harms.

Although this is certainly an important question that needs to be resolved, we suggest that considerations of benefit and harm should also include the indirect effects of neuraminidase inhibitors. Specifically, several studies[5-9] have reported fewer secondary cases among close contacts of index cases receiving neuraminidase inhibitors. These reports suggest that in addition to the possible direct benefits to the patient receiving neuraminidase inhibitors, the treated person might also benefit from a reduction in infections in close contacts. For instance, a reduction of days of work lost due to having to stay home with a sick contact or reduced medical costs for a household because of reduced physician visits can be considered direct benefits to the treated person, caused

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by the indirect effect of the treatment on transmission. Although this indirect effect is commonly included in epidemic transmission models, few cost-effectiveness studies[10–12] consider it, and the potential benefits of indirect effects seem to be missing from the present benefit–harm discussion of neuraminidase inhibitors.

We argue that the standard harm–benefit considerations that guide test and treatment administration should be broadened to include potential benefits and harms that an individual might experience by altering outcomes in others. As such, although further investigation and a better understanding of the benefits and risks of neuraminidase inhibitors to the individual due to direct effects is crucial, the harms and benefits of indirect effects of neuraminidase inhibitors should also receive further detailed study. Most important in that respect is to better quantify the potential effect of neuraminidase inhibitors in reducing transmission than is done at present. Although some evidence[5–9] seems to point to a beneficial effect of transmission reduction, stronger and more rigorous studies and analysis are still needed.[2,13,14]

The decision to prescribe or not prescribe neuraminidase inhibitors to an individual should not only consider their health status, resultant costs, and potential benefits, but also potentially affected contacts and, if possible, society at large. Ideally, this would include considerations such as the effect of widespread use of neuraminidase inhibitors on resistance emergence. Unfortunately, a detailed cost–benefit quantification of the effect of neuraminidase inhibitor use on resistance emergence seems almost impossible. However, detailed cost–benefit calculations, factoring in direct and indirect effects as discussed here are feasible and, we argue, should play a more prominent role in decision making for any intervention with indirect effects.

We declare no competing interests.

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1 Ebell MH, Call M, Shinholser J. Effectiveness of oseltamivir in adults: a meta-analysis of published and unpublished clinical trials. *Fam Pract* 2013; **30:** 125–33.
2 Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2014; **4:** CD008965.
3 Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med* 2014; **2:** 395–404.
4 Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet* 2015; published online Jan 30. http://dx.doi.org/10.1016/S0140-6736(14)62449-1.
5 Halloran ME, Hayden FG, Yang Y, Longini IM, Monto AS. Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials. *Am J Epidemiol* 2007; **165:** 212–21.
6 Yang Y, Halloran ME, Longini IM. A Bayesian model for evaluating influenza antiviral efficacy in household studies with asymptomatic infections. *Biostatistics* 2009; **10:** 390–403.
7 Nishiura H, Oshitani H. Household transmission of influenza (H1N1-2009) in Japan: age-specificity and reduction of household transmission risk by zanamivir treatment. *J Int Med Res* 2011; **39:** 619–28.
8 Carrat F, Duval X, Tubach F, et al. Effect of oseltamivir, zanamivir or oseltamivir-zanamivir combination treatments on transmission of influenza in households. *Antivir Ther* 2012; **17:** 1085–90.
9 Pebody RG, Harris R, Kafatos G, et al. Use of antiviral drugs to reduce household transmission of pandemic (H1N1) 2009, United Kingdom. *Emerg Infect Dis* 2011; **17:** 990–99.
10 Lugnér AK, Postma MJ. Mitigation of pandemic influenza: review of cost-effectiveness studies. *Expert Rev Pharmacoecon Outcomes Res* 2009; **9:** 547–58.
11 Smith JR, Rayner CR, Donner B, Wollenhaupt M, Klumpp K, Dutkowski R. Oseltamivir in seasonal, pandemic, and avian influenza: a comprehensive review of 10-years clinical experience. *Adv Ther* 2011; **28**: 927–59.
12 Postma MJ, Beardsworth P, Wilschut JC. Cost effectiveness of oseltamivir treatment of influenza: a critique of published methods and outcomes. *J Med Econ* 2008; **11:** 743–68.
13 Ng S, Cowling BJ, Fang VJ, et al. Effects of oseltamivir treatment on duration of clinical illness and viral shedding and household transmission of influenza virus. *Clin Infect Dis* 2010; **50:** 707–14.
14 Goldstein E, Cowling BJ, O'Hagan JJ, et al. Oseltamivir for treatment and prevention of pandemic influenza A/H1N1 virus infection in households, Milwaukee, 2009. *BMC Infect Dis* 2010; **10:** 211.

Responding to the Syrian health crisis: the need for data and research

As described in the News report about the ongoing crisis in Syria[1] in *The Lancet Respiratory Medicine*, the health situation of internally displaced people and refugees in Syria is severe and continues to deteriorate. The author called attention to many of the challenges faced by international organisations in addressing the health situation of internally displaced people and refugees in the country.

However, we believe that urgent policy and research attention needs to be given to the generation of timely and high-quality evidence on the effectiveness of the humanitarian health response, the capacity of health systems within Syria, and the issue of non-communicable diseases among internally displaced people and refugees. Media outlets and decision makers have tended to focus on disorders such as leishmaniasis and poliomyelitis, rather than on non-communicable diseases. We agree with WHO and other humanitarian agencies when they act to stem the incidence of poliomyelitis in Syria. However, many less visible and untreated non-communicable disorders, such as cardiovascular disease, cancer, diabetes, and mental health issues are also highly prevalent in Syria and have caused the deaths and disability of thousands of internally displaced people and refugees from Syria.

As with Iraq since 2003, the situation in Syria shows how conflict in middle-income countries affects the burden of non-communicable diseases.[2] As a result, the humanitarian response in this new health context is shifting from the delivery of services related to communicable diseases to intervention for non-communicable diseases. Countries affected by the