LETTERS

Letters are selected from rapid responses posted on bmj.com. After editing, all letters are published online (www.bmj.com/archive/sevendays) and about half are published in print
To submit a rapid response go to any article on bmj.com and click "respond to this article"

NEWS STORY ON TAMIFLU STUDY

PRIDE study's principal author responds to *BMJ* news story

On 19 March 2014, researchers from the PRIDE (Post-pandemic Review of anti-Influenza Drug Effectiveness) Consortium published the first outputs from a project investigating the effectiveness of neuraminidase inhibitors against outcomes of public health importance during the 2009 flu pandemic in the *Lancet Respiratory Medicine*.[1 2] The headline results suggested that neuraminidase inhibitors were associated with statistically significant reductions in mortality: overall adjusted odds ratio 0.81 (95% CI 0.70 to 0.93; P=0.0024) versus no treatment and 0.50 (0.37 to 0.67; P<0.0001) if treatment was started within two days of symptom onset.

Within 48 hours, *The BMJ* published an article written by a staff journalist, which claimed that the new study "was based on flawed analysis."[3] Zosia Kmietowicz had contacted Mark Jones, University of Queensland, who is working with the Cochrane Collaboration on another project related to neuraminidase inhibitors. In turn, Jones had provided a detailed statistical critique of the PRIDE study, which formed the centrepiece of Kmietowicz's article. The PRIDE Consortium was not forewarned about the article and, more importantly, not offered any a priori right of reply, as would normally be the case during post-publication correspondence. Faced with such a one sided critique of its work, the PRIDE Consortium had no option but to post its initial rebuttal in *The BMJ*.[4] There has since been a further critique from Jones and a further statistical rebuttal from the PRIDE Consortium.[5 6]

Thus, the correspondence and debate relating to a major publication in a Lancet Group paper has been played out in the pages of *The BMJ*, fronted by an entirely one sided article from a staff journalist on *The BMJ*. The major question here seems to be the propriety of *The BMJ* and Dr Jones in going beyond the reasonable response to a press release, by asking potential opponents for a detailed statistical critique without offering the authors of the study any right to reply alongside. A more conventional and considerably more ethical approach would have been to submit correspondence post-publication to the *Lancet Respiratory Medicine*, which could then have considered the response in the normal way, including offering the PRIDE Consortium a realistic period of time to consider the critique and write a rejoinder.

Jonathan S Nguyen-Van-Tam clinical professor of health protection, and senior author, PRIDE Consortium, University of Nottingham, Clinical Sciences Building, City Hospital, Nottingham NG5 1PB, UK
jonathan.van-tam@nottingham.ac.uk

Competing interests: I am senior author of the paper that was critiqued.

1 University of Nottingham, Health Protection and Influenza Research. PRIDE Study: Post-pandemic Review of anti-Influenza Drug Effectiveness. www.nottingham.ac.uk/research/groups/healthprotection/projects/pride.aspx.
2 Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TSA, Al Mamun A, 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; published online 19 Mar.
3 Kmietowicz Z. Study claiming Tamiflu saved lives was based on "flawed" analysis. *BMJ* 2014;348:g2228. (19 March.)
4 Myles PR, Leonardi-Bee J; PRIDE research consortium investigators. Re: Authors' response to Dr Jones's critique of the study by Muthuri et al (2014) [electronic response to Kmietowicz Z. Study claiming Tamiflu saved lives was based on "flawed" analysis]. *BMJ* 2014. www.bmj.com/content/348/bmj.g2228/rr/691879.
5 Jones M. Reply to Puja R Myles and Jo Leonardi-Bee [electronic response to Kmietowicz Z. Study claiming Tamiflu saved lives was based on "flawed" analysis]. *BMJ* 2014. www.bmj.com/content/348/bmj.g2228/rr/692120.
6 Myles PR, Leonardi-Bee J; PRIDE research consortium investigators. Further clarifications from authors of the Muthuri et al (2014) paper in response to Dr Jones's second critique [electronic response to Kmietowicz Z. Study claiming Tamiflu saved lives was based on "flawed" analysis]. *BMJ* 2014. www.bmj.com/content/348/bmj.g2228/rr/692897.

Cite this as: *BMJ* 2014;348:g2935

∴ Jonathan Nguyen-Van-Tam questions the way *The BMJ* handled its news reporting of his paper. By way of background, *The BMJ* regularly carries news reports on studies published in other journals, and our reports usually include comments from other researchers, which are often critical of the study. We do not routinely offer a right of reply to the study's authors. However, given the extent of the critique in this case and the title of the news story, I can see that a right of reply would have been appropriate. I thank the authors for their response to the news report, and I hope readers will read the full correspondence in the accompanying rapid responses.—FIONA GODLEE, editor, *The BMJ*

The BMJ's activism will ultimately harm its reputation

Historically, medical journals have served as neutral forums for the presentation and discussion of scientific issues. *The BMJ* has in recent years rejected this historical model by taking an activist role in advocacy campaigns such as AllTrials and the current investigations of the regulatory history of Tamiflu. Whether *The BMJ* is ultimately found to be on the "right" side of these issues, I believe that the inherent conflict of interest between the journal's putative role as a neutral forum for scientific discussion and the advocacy roles taken by its editors will harm the journal's reputation.

The current episode, in which an opinionated criticism of a paper on one side of the Tamiflu debate was written with the actively solicited input of those on the other side of the scientific debate,[1] illustrates the problem caused by these conflicts of interest. The authors of the paper were not even given the opportunity to rebut the journal's criticism in the same issue in which the criticism appeared.

Given this level of hardball partisanship, to what extent can any article published in *The BMJ* be considered truly peer reviewed? Obviously, the editors have the power to choose reviewers who will render decisions that they agree with. And it's obvious that on many of these issues the editors have a dog in the fight.

In the long run, the reputation of the journal will suffer.

John A Tucker freelance scientific writer, 7039 Santa Fe Canyon Place, San Diego, CA 92129, USA
john.alan.tucker@gmail.com

Competing interests: None declared.

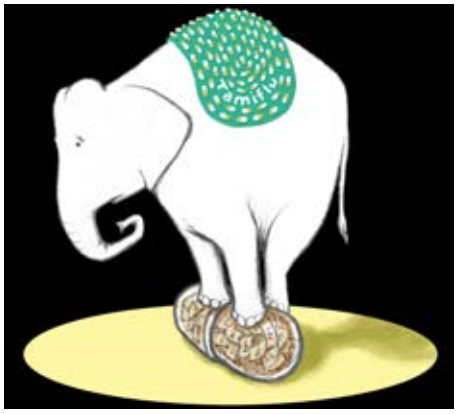
1 Kmietowicz Z. Study claiming Tamiflu saved lives was based on "flawed" analysis. *BMJ* 2014;348:g2228. (19 March.)

Cite this as: *BMJ* 2014;348:g2976

OSELTAMIVIR FOR INFLUENZA

No place for antiviral drug distribution in a flu pandemic

The BMJ and Cochrane Collaboration showed serious generic failings in the system of publishing full trial evidence about oseltamivir for flu.[1] We remain concerned, however, that the insights of service providers during the 2009-10 pandemic have not been given the same public consideration.[2]



Even the selective evidence available in 2009 cannot justify the financial and public health cost of the government maintaining its oseltamivir orthodoxy during the H1N1 outbreak in the face of evidence demonstrating the indefensibility of such a position. Drugs that might be effective in clinical trials can also be inefficient, or fail to deliver the patient benefit predicted by trial results, when subject to the limitations of general service use. Frontline responders in the pandemic witnessed the wanton abandonment of first principles such as isolation, basic control of infection measures, and clinical assessment in favour of stubborn insistence on managing "England as a single epidemiological unit." The irrational maintenance of the "containment" phase led directly to perverse and damaging interventions and over-reliance on antiviral drugs in mass prophylaxis, especially in schools. Antiviral drug centres became loci for the spread of infection as thousands of symptomatic and sub-clinical cases—flu can be spread by symptom-free patients[3 4]—and unaffected contacts convened for a "wonder drug," with serious potential side effects,[1] which would now seem to be no more effective in pandemic management than paracetamol.[5]

Not to underpin current planning for pandemics and any subsequent responses would be irresponsible. Antiviral drug distribution has no place in a pandemic on current evidence of the drugs' effectiveness for treatment or mass prophylaxis, and with the increased risk of spread of infection from directing populations to distribution centres.

Patrick J Saunders professor of public health, Faculty of Health Sciences, School of Social Work, Allied and Public Health, Staffordshire University, Stafford ST18 0AD, UK
patricksaunders@sky.com
John Middleton former director of public health, Sandwell, Coventry CV3 2AB, UK

Competing interests: None declared.
Full response at: www.bmj.com/content/348/bmj.g2545/rr/694663

1 Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;348:g2545
2 Chambers J, Barker K, Rouse A. Reflections on the UK's approach to the 2009 swine flu pandemic: conflicts between national government and the local management of the public health response. *Health Place* 2012;18:737-45.
3 Centers for Disease control. Additional information about vaccination of specific populations. Influenza prevention and control recommendations. www.cdc.gov/flu/professionals/acip/specificpopulations.htm l.
4 Chao D-Y, Cheng K-F, Li T-C, Wu T-N, Chen C-Y, Tsai CA, et al. Serological evidence of subclinical transmission of the 2009 pandemic H1N1 influenza virus outside of Mexico. *PLoS ONE* 2012;6:e14555.
5 Gallagher J. Tamiflu: millions wasted on flu drug, claims major report. BBC News 2014. www.bbc.co.uk/news/health-26954482.

Cite this as: *BMJ* 2014;348:g2955

USING DATA ON PATIENT EXPERIENCE

Patient feedback as a way to improve quality of care

We agree with Coulter and colleagues that patient experience data should be used more effectively, but introducing another NHS data collating/analysing body could be counterproductive if the implicit assumption is that all data are (more or less) equally valid.[1] Poorly collected data detract from scientifically valid data. The recent proliferation of "rapid" patient feedback focuses attention on quick fixes at the expense of tackling long term problems.

Annual national patient surveys from the Care Quality Commission (CQC) conform to recognised methodological standards. Samples are representative of the patient population; reminders to non-responders maximise response rates; good response rates are achieved from ethnic minorities and elderly patients; questions are pre-tested for comprehensibility; patients may add their own comments; and data are not collected by ward staff. Many other methods of gathering patient experience data (such as the friends and family test) meet few of those criteria. The CQC's surveys could be improved if they were ward specific (to counter "that doesn't happen on my ward"), but, in common with other methods, their main failing is too little emphasis on actively feeding back findings to the people responsible for delivering day to day care.

Our recent pilot randomised controlled trial showed that facilitated meetings with nurses to discuss their own ward specific patient survey results had a highly significant impact on survey scores, whereas written survey results alone had no impact. The meetings often entailed difficult conversations: some nurses were reluctant to believe negative feedback; others were hurt, defensive, or critical of patients in return. Patients' comments were more effective than statistics in capturing nurses' interest, but concomitant descriptive statistics were needed to distinguish isolated incidents from general problems.[2]

Our main point is that, whereas Coulter and colleagues recommend collating and triangulating data, we advocate further trials to test methods of using patient feedback to improve the quality of care.

Rachel J Reeves principal research fellow
r.reeves@greenwich.ac.uk
Elizabeth West professor of applied social research, School of Health and Social Care, University of Greenwich, London SE9 2UG, UK

Competing interests: None declared.
Full response at: www.bmj.com/content/348/bmj.g2225/rr/694618.

1 Coulter A, Locock L, Ziebland S, Calabrese J. Collecting data on patient experience is not enough: they must be used to improve care. *BMJ* 2014;348:g2225. (27 March.)
2 Reeves R, West E, Barron D. Facilitated patient experience feedback can improve nursing care: a pilot study for a phase III cluster randomised controlled trial. *BMC Health Serv Res* 2013;13:259.

Cite this as: *BMJ* 2014;348:g2953

VITAMIN D AND CAUSE SPECIFIC DEATH

Cancer: vitamin D affects mortality more than incidence

Chowdhury and colleagues' meta-analysis of cancer specific incidence and mortality rates with respect to bottom versus top third of baseline 25-hydroxyvitamin D levels found higher relative risks for those with cancer at time of enrolment than those without.[1] The implication of this finding is that vitamin D has a much stronger impact on survival after developing cancer than on reducing the risk of developing cancer.

Findings of reduced risk of cancer from ecological studies are much stronger than those of observational studies, partly because of larger numbers of cases, and partly because of the stronger effect of vitamin D on cancer mortality rates than on cancer incidence rates.[2] It is reasonable that vitamin D might have a greater effect on cancer mortality than on incidence because there are many risk factors for cancer incidence but only a few natural mechanisms in the body, such as vitamin D, that reduce the progression and metastasis of cancer.[2]

Clinical trials are therefore needed to investigate the effect of eliminating vitamin D deficiency on survival in patients with cancer. Guidelines for vitamin D randomised controlled trials were recently proposed.[3] In addition, a committee of the National Institute of Sciences-Institute of Medicine and a guideline of the Endocrine Society of the United States have recommended vitamin D doses for adults from 2000-10 000 IU/day.[4 5] On the basis of these guidelines, measurement of serum and supplementation (if needed) should be considered for patients with cancer with 25-hydroxyvitamin D levels <100 nmol/L. The dose should be tailored to individual patients on the basis of baseline serum 25-hydroxyvitamin D level before vitamin D is begun.

William B Grant researcher, Sunlight, Nutrition and Health Research Center, San Francisco, CA 94164-1603, USA
wbgrant@infionline.net
Cedric F Garland adjunct professor, Division of Epidemiology, Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA, USA

Competing interests: WBG receives funding from Bio-Tech Pharmacal (Fayetteville, AR), the Sunlight Research Forum (Veldhoven), and the UV Foundation (McLean, VA). CFG has none to declare.

Full response at: www.bmj.com/content/348/bmj.g1903/rr/694470.

1 Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-de-Jong JC, et al. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ* 2014;348:g1903. (1 April.)
2 Moukayed M, Grant WB. Molecular link between vitamin D and cancer prevention. *Nutrients* 2013;5:3993-4023.
3 Heaney RP. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. *Nutr Rev* 2014;72:48-54.
4 Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011;96:53-8.
5 Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96:1911-30.

Cite this as: *BMJ* 2014;348:g2862

Vitamin D supplements do not reduce mortality risk

In their meta-analysis of 22 randomised controlled trials (RCTs), Chowdhury and colleagues report that, overall, vitamin D supplements had no effect on mortality, but a subgroup analysis suggested mortality was reduced in 14 trials of vitamin D_3 and not in eight trials of vitamin D_2.[1] However, three of the trials classified as vitamin D_3 trials actually studied calcitriol (1,25-dihydroxyvitamin D_3). Another trial compared the effects of an exercise programme plus vitamin D_3 with a control group that did not receive an exercise programme. Results from RCTs of active metabolites of vitamin D or multifactorial interventions cannot be ascribed to vitamin D_3.

When these four trials are removed from Chowdhury and colleagues' analyses, the pooled relative risk for all 18 trials is 0.98 (95% CI 0.92 to 1.06) and for the 10 vitamin D_3 trials it is 0.92 (0.84 to 1.02). Therefore, these analyses do not provide evidence for an effect of vitamin D (or vitamin D_3) on mortality.

In a recent trial sequential meta-analysis of the effect of vitamin D (with or without calcium supplements) on mortality, we included seven other RCTs of vitamin D alone, and seven of calcium and vitamin D compared with calcium, in addition to the trials analysed by Chowdhury and colleagues.[2] The most recent Cochrane review included several other potentially relevant RCTs.[3] There are many meta-analyses on vitamin D and health outcomes: we identified 45 meta-analyses on falls or fractures and 12 on mortality in a PubMed search. The differences between the results of these meta-analyses seem largely due to the methods adopted by the authors, such as their choice of studies that are included, how co-administration of calcium is dealt with, and how the studies are divided in subgroup analyses.

Mark J Bolland associate professor of medicine
m.bolland@auckland.ac.nz
Andrew Grey associate professor of medicine
Ian R Reid professor of medicine, Department of Medicine, University of Auckland, Private Bag 92019, Auckland, New Zealand

Competing interests: None declared.

Full response with references at: www.bmj.com/content/348/bmj.g1903/rr/694048.

1 Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-de-Jong JC, et al. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ* 2014;348:g1903. (1 April.)
2 Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. *Lancet Diabetes Endocrinol* 2014;2:307-20.
3 Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev* 2014;1:CD007470.

Cite this as: *BMJ* 2014;348:g2860

Authors' reply

We agree with Grant and Garland that, although existing ecological studies support the findings of our meta-analysis of observational studies, further work—especially that involving well powered randomised intervention studies—is needed. However, the respective pooled risk ratios that we reported by combining the primary and secondary prevention cohorts are based on indirect comparisons (only a subset of studies provided mortality risk data on people with pre-existing disease).

As Bolland and colleagues note, the overall estimates from the vitamin D_3 randomised controlled trials were indeed presented as a combination of both active and inactive vitamin D_3 supplements, given a lack of power in each component in isolation. We also included a study that evaluated the effects of vitamin D_3 alone without concurrent administration of other pharmacological interventions (which was similarly kept as a vitamin D alone study in the earlier Cochrane report).[1] Nonetheless, when this study and the other three calcitriol trials were removed from the analyses,[2-4] there was no significant effect of "any vitamin D supplementation" on mortality (which remains consistent with our original results). The pooled effect estimate for the 10 vitamin D_3 trials became slightly attenuated (0.91, 95% CI 0.82 to 1.00) in our calculation; however, this apparent inverse effect differed significantly from the corresponding pooled estimate of vitamin D_2 (P from meta-regression analysis=0.03, for a comparison between vitamin D_3 and vitamin D_2 trials). That said, we agree with Bolland and colleagues that the selection criteria (such as randomised *v* non-randomised, with calcium supplementation *v* without) and decisions on subgroup analyses vary across reviews on this topic, and this may explain the different findings across these reports. However, as was discussed in our paper (and the accompanying editorial), all these reviews (including ours) are based on largely overlapping trials of mostly high risk, elderly populations (with an average age >75 years in all trials combined). Therefore, before any policy formulation, further large scale and sufficiently prolonged trials with large samples derived from the general population will be required.

Rajiv Chowdhury cardiovascular epidemiologist, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge CB1 8RN, UK
Oscar H Franco professor, Department of Epidemiology, Erasmus MC, Rotterdam, Netherlands
o.franco@erasmusmc.nl
On behalf of Setor Kunutsor, Anna Vitezova, Clare Oliver-Williams, Susmita Chowdhury, Jessica C Kiefte-de-Jong, Hassan Khan, Cristina P Baena, Dorairaj Prabhakaran, Moshe B Hoshen, Becca S Feldman, An Pan, Laura Johnson, Francesca Crowe, and Frank B Hu

Competing interests: None declared.

1 Campbell AJ, Robertson MC, La Grow SJ, Kerse NM, Sanderson GF, Jacobs RJ, et al. Randomised controlled trial of prevention of falls in people aged ≥75 with severe visual impairment: the VIP trial. *BMJ* 2005;331:817.
2 Grady D, Halloran B, Cummings S, Leveille S, Wells L, Black D, et al. 1,25-dihydroxyvitamin D_3 and muscle strength in the elderly: a randomized controlled trial. *J Clin Endocrinol Metab* 1991;73:1111-7.
3 Gallagher JC. The effects of calcitriol on falls and fractures and physical performance tests. *J Steroid Biochem Mol Biol* 2004;89-90:497-501.
4 Beer TM, Ryan CW, Venner PM, Petrylak DP, Chatta GS, Ruether JD, et al. Double-blinded randomized study of high-dose calcitriol plus docetaxel compared with placebo plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT Investigators. *J Clin Oncol* 2007;25:669-74.

Cite this as: *BMJ* 2014;348:g2931