Does Evidence Matter in Evidence Based Medicine (EBM)?

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On Septenber 6, 2012, an unprecedented coalition of EBM and public health scientists, the chamber of physicians of Berlin[1], the anti-corruption organization Transparency International[2] and the Charité Universitätsmedizin Berlin[3] invited Peter Doshi from Johns Hopkins University School of Medicine, to present his research on the science and policy of pandemic influenza and influenza antivirals [4]. Doshi, a reviewer for the Cochrane Collaboration systematic review on neuraminidase inhibitors, argued that influenza is a disease that has been understood primarily through the marketing efforts of public health professionals, and that there are major problems in the evidence base for influenza vaccines and antivirals. Doshi noted that prior to 2009, around $8 billion worth of oseltamivir (Tamiflu) was stockpiled by governments in preparation for an influenza pandemic with assumptions about the proven effectiveness of the drug, but those assumptions remain unproven. Doshi asked how this could happen in a world in which public health decision is believed to be science-based.

In front of clinicians, EBM and public health scientists, Doshi used original policy documents by the World Health Organization (WHO) [5], [6], [7], [8] and other national pandemic plans [9], [10], to show that claims made about viral pandemic threats and their control through preparedness measures[11] including mass vaccination and the stockpiling of antiviral agents such as oseltamivir were all but evidence-based[12]. Documented close ties between members of the Emergency Committee of WHO,[13] which was responsible for declaring a pandemic and for decision-making during a pandemic, and the pharmaceutical industry only added to the lack of trust in the objectivity and independence of official decision-making structures [14] [15][16][17].

Doshi highlighted the complete absence of public health bodies carrying out an independent review of the oseltamivir evidence base prior to stockpiling. Instead of examining the data themselves, influential bodies such as the US Department of Health and Human Services and the Centers for Disease Control and Prevention (CDC) pointed to industry authored publications in medical journals—in particular, one non-systematic review published in 2003 in Archives of Internal Medicine [18].

However, this study, a pooled analysis of ten randomized controlled trials of which eight remain unpublished, was later shown to be seriously flawed[19][20]. Oseltamivir's manufacturer, Roche, also admitted some of its published studies were ghostwritten[16].

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Doshi explained how their Cochrane team led by Dr. Tom Jefferson in Rome, concluded that journal publications were unreliable, and instead decided to base their systematic review upon far more detailed documents called Clinical Study Reports. After requesting these reports from the European Medicines Agency (EMA) under its new freedom of information policy (2010), the Cochrane investigators were able to compare the reports (more than 22,000 unique pages), submitted to EMA by Roche for marketing approval of oseltamivir in 2002, with the published results appearing in prestigious medical journals. This revealed large inconsistencies between the published information and the previously secret internal company reports.

Of public health relevance, the Cochrane team found no evidence for a preventive effect on spread of the virus or decreased risk of severe complications like hospitalization. (Incidentally, the U.S. Food and Drug Administration (FDA) arrived at the same conclusions in 2000, and in fact language documenting the lack of evidence was inserted into the US product labeling). Even more disquieting: despite publicly promising to release full study reports, Roche has kept the study protocols and the bulk of its study reports afar from public scrutiny.

Without the EMA's new policy on access to documents, independent scientists would not be able to access these detailed data. But Doshi noted that reports EMA provided the Cochrane team were themselves incomplete because EMA itself had not requested the full reports from Roche.

Obviously, selective reporting, attrition and publication bias are well known problems in the world of medical publishing, and have partially been addressed by mandatory prospective registration of clinical trials worldwide. However, the amount of pharmaceutical industry data and information in relation to oseltamivir kept inaccessible to independent review, was astounding even to experienced researchers in this particular field like Jefferson and Doshi.

The conclusion of the public debate following Doshi's presentation was straightforward: selective reporting, and the omission or suppression of data, may be routinely utilized, unintentionally or intentionally, concealing an accurate understanding of a study. Those relying on evidence-based medicine need to urgently question whether current established EBM methods of evidence appraisal, focussing on journal publications, are able to distinguish distorted clinical trial results from valid findings. In fact, the validity of EBM and related guidelines, as long as they are solely based on publications in peer-reviewed journals (or other data inaccessible to independent scrutiny), must be questioned and put under review.

Calls were made to urgently address this problem. Should it be left to the scientific community, publishers or even to the for-profit industry? What should be done if intentional selective reporting is used for individual gains or economic benefits, and which preventive actions or sanctions, respectively, against such abuses should be implemented?

The oseltamivir story raised deep questions about the accuracy and integrity of decisions of regulatory agencies and public health bodies. Officers from regulatory agencies in attendance of the debate claimed that governmental institutions are uniquely positioned to ensure the objective assessment of and recommendations about medical interventions for the well-being of the population. However, the case of

influenza and oseltamivir reveals that additional control mechanisms are necessary to prevent regulatory or public health agencies from ignoring concerns[21] [22] of independent scientists and civil society organizations. Even the FDA's official "Warning Letter" to Roche in the year 2000, stating that Tamiflu has not been shown to reduce serious complications of influenza [23] was apparently totally ignored by those in other parts of the government who made the decision to stockpile the drug, citing Roche-authored publications as the scientific "evidence" to support claims that oseltamivir would reduce complications and hospitalizations [24].

It was suggested that the first and most publicly relevant measure should be the urgent revision of public health recommendations such as the international and national pandemic influenza plans, and secondly, to stop stockpiling of a drug still unproven to prevent the spread of influenza or its complications.

Finally, a democratic and transparent control mechanism for regulatory and public health agencies and related expert committees is urgently needed. A call for public financing of research in the public interest and with unhindered access to complete datasets for independent scientific evaluation, evolved in the debate as the only possible way forward to allow objective analysis and unbiased publication of clinical trial results.

It was acknowledged that the recent efforts by EMA regulators to provide access to documents in their possession (including those submitted by industry, such as Clinical Study Reports and study protocols) [25] were a huge step forward towards ensuring transparency in medical research.

For spreading the debate in the wider medical and scientific community, as well as to gain broader public support, the authors have drafted the "Berlin Declaration 2012" - together with a signing list - aiming to promote and reinstitute the integrity of scientific publishing, EBM and public health decision making.

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