Saturday 7 June 2003

BMJ

Preventing and treating influenza

Neuraminidase inhibitors are clinically effective but have limitations

WHO estimates that seasonal influenza epidemics result in three to five million cases of severe illness and 250 000 to 500 000 deaths each year in the industrialised world alone. Although vaccination remains the most important measure for reducing this sizeable public health burden, the influenza virus neuraminidase inhibitors, zanamivir and oseltamivir, have been welcomed as long awaited additional tools for treatment and prevention. However, in terms of meeting public health objectives, which include clinical effectiveness in high risk groups and preparedness for the next influenza pandemic, they have important limitations.

As documented in the paper by Cooper et al p 1235) in this issue, neuraminidase inhibitors are clinically effective for the treatment of influenza in otherwise healthy adults and children as well as for prevention of the disease.[1] When used as a treatment, they can reduce the duration of uncomplicated disease by about one day, and the likelihood of complications requiring antimicrobial treatment. Taken prophylactically they can decrease the likelihood of developing influenza by 70-90% depending on the target population and duration of use. Baseline data for the surveillance of viral susceptibility to neuraminidase inhibitors have been established—initial data have produced no evidence of naturally occurring resistance in any of the isolates tested.[2]

Despite these promising features many obstacles limit the role of neuraminidase inhibitors as public health tools. High cost is one factor. Another obstacle is the paucity of data on efficacy in preventing serious influenza related complications and mortality in groups at highest risk, including elderly people and people with underlying disease—the groups responsible for the greatest medical and economic burden of influenza and hence of greatest public health concern.

Neuraminidase inhibitors were introduced into clinical practice from 1999 to 2002 but are currently used in only a few countries. In view of their limitations they are only adjuncts to influenza vaccination. Around three quarters of all prescriptions are issued in Japan, with the remainder concentrated in the United States and only a very small number issued elsewhere. Oseltamivir is by far the most widely used neuraminidase inhibitor, mainly because of ease of application.

Community studies show that seasonal prophylactic use of neuraminidase inhibitors in healthy adults, administered after exposure in households and in residential care, would be clinically effective. However, when economic factors are considered vaccination seems to have a much more favourable ratio of cost to benefit.[3]

Because of costs and an efficacy that also depends on the prevalence of influenza in the population, neuraminidase inhibitors are recommended for treatment only during the influenza season when most infections of the upper respiratory tract are due to influenza viruses. Such a strategy automatically excludes most countries in tropical areas, where sporadic cases of influenza occur year round with no distinct season. In addition, countries in temperate areas require efficient community based virological surveillance schemes to indicate to general practitioners the beginning of the influenza season. Rapid influenza tests are available. However, their lack of sensitivity limits their use to the influenza season.

For all these reasons, currently available neuraminidase inhibitors cannot replace annual influenza vaccination, which remains the most effective means of reducing the medical and economic impact of influenza. Unfortunately knowledge about the medical benefits of influenza vaccination and its favourable cost:benefit ratio compared with other prevention strategies has not been translated into effective immunisation programmes in most countries. At present, only around 50 countries, mainly in the industrialised world, have policies for influenza immunisation, and vaccination coverage often reaches only 10-20% of people in groups at high risk. Coverage rates in developing countries are often negligible. In addition, immunisation coverage of healthcare workers in direct contact with elderly people is often low despite strong evidence of their role in contributing to institutional outbreaks as well as their own vulnerability to infection.

Recognising the significance of influenza immunisation as a public health strategy, the World Health Assembly of the World Health Organization has in May 2003 approved a resolution calling on countries that have national influenza vaccination policies to implement strategies to increase vaccination coverage of all people at high risk to at least 50% by 2006 and 75% by 2010. Countries without national influenza vaccination policies should assess the disease burden and economic impact of annual influenza epidemics as a basis for framing and implementing influenza prevention policies within the context of other national health priorities.[4]

Papers p 1235

BMJ 2003;326:1223–4

Considering the annual death toll and morbidity from influenza and the need for efficient and affordable antivirals during the first phase of the next influenza pandemic, cost efficient and clinically effective treatment and prophylactic tools are urgently needed. Neuraminidase inhibitors are clinically effective complements to the current influenza intervention tools. However, costs and lack of data on their effectiveness in the groups most severely affected by influenza limit their use in many industrialised countries and make them largely unaffordable in developing countries. Promising research is under way to develop new neuraminidase inhibitors that are more efficacious, cost less, and are simpler to prescribe. It is to be hoped that they are available before the next pandemic strikes.

Klaus Stöhr *project leader, WHO Global Influenza Programme*

World Health Organization, Avenue Appia, CH-1211 Geneva, Switzerland (stohrk@who.int)

Competing interests: None declared.

1 Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner DA, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2003;326:1235-40.
2 McKimm-Breschkin JL, Trivedi T, Hampson AH, Hay A, Klimov A, Tashiro M, et al. Neuraminidase sequence analysis and susceptibilities of influenza virus clinical isolates to zanamivir and oseltamivir. *Antimicrobial Agents and Chemotherapy* 2003 (in press).
3 Scuffham PA, West PA. Economic evaluation of strategies for the control and management of influenza in Europe. *Vaccine* 2002;20:2562-78.
4 World Health Organization. Fifty-Sixth World Health Assembly. Prevention and control of influenza pandemics and annual epidemics (agenda item 14.14). Geneva: WHO, 26 May 2003. (Draft A56/63.) www.who.int/gb/EB_WHA/PDF/WHA56/ea5663.pdf (accessed 28 May 2003).

Editorial misconduct

Medical editors need effective self regulation

Education and debate p 1262

As with members of any group—be they doctors, politicians, or cardinals—some editors misbehave. Managing their misbehaviour is complicated by widespread devotion to the principle of editorial freedom, a devotion that is energetically promoted by editors. When an organisation takes the nuclear option of firing its editor—as the American Medical Association did in 1999—the roof falls in.[1 2] How can the circle of editorial independence and the need to discipline erring editors, of whom there are many, be squared? The answer may be self regulation, some sort of general medical journalists council.

Regular readers of the *BMJ* will imagine that it is my own misbehaviour that prompts me to meditate on the theme of editorial misconduct. My sins in the past two months include publishing an obituary seen by many as a hatchet job,[3 4] publishing research funded by the tobacco industry that implied that passive smoking did not kill,[5] carrying an offensive cover on the journal that depicted doctors as pigs, drug company representatives as lizards, and a bemused patient as a guinea pig, and publishing a study highly sceptical of the private finance initiative in the run up to the Scottish parliamentary elections.[6] The obituary sin has been referred to the Press Complaints Commission, a body that provides self regulation for the British press, and I will of course accept its ruling. The commission wrestles mostly, however, with the monster that is the British tabloid press and is not well suited to pass judgment on more scientific and professional issues.

It is not my own sins that prompt this editorial but rather the story of how *Human Immunology* fired its guest editor for publishing an article with political content but left the editor in chief in post despite some doubtful behaviour (p 1262).[7] Antonio Arnaiz-Villena, a professor of immunology and cell biology in Madrid, was asked by the editor of *Human Immunology*, Nicole Suciu-Foca, a professor in New York, to edit a theme issue on anthropology and genetic markers. He was given little or no guidance on what was expected. Nor was it clear whether the language would be (or actually was) copy edited—despite English not being the first language of most of the contributors, including the guest editor.

The problems arose with Arnaiz-Villena's keynote paper for the issue, which concluded that Jews and Palestinians are genetically very close and that their "rivalry is based on cultural and religious, but not genetic, differences." It wasn't the science that caused the problem but words and phrases in the article that seemed political—particularly in the highly emotional climate that followed the 11 September attacks on New York and Washington (the issue was published in November 2001). Karen Shashok—an American who lives in Spain and works as a translator and editor—argues that most of the problems arose from lapses in translation and editing rather than political intent.[7] Whatever the cause the response was dramatic. The editor fired the guest editor and had the article retracted from Medline and deleted from the online edition of the journal. Subscribers were even invited "to physically remove the pages" from their copies of the journal. Was this an over-reaction? Was the editor making the guest editor the scapegoat for her own failures? The editor, the owners (the American Society of Histocompatibility and Immunogenetics), and the publishers (Elsevier Science) have not answered these questions, and this might be an ideal case to refer to an international medical scientific press council.

Doug Altman (a statistical adviser to the *BMJ*), Iain Chalmers (one of the founders of the Cochrane Collaboration), and Andrew Herxheimer (a former editor of the *Drug and Therapeutics Bulletin*) advocated the setting up of such a council more than a decade

BMJ 2003;326:1224–5