LETTERS

We select the letters for these pages from the rapid responses posted on bmj.com favouring those received within five days of publication of the article to which they refer. Letters are thus an early selection of rapid responses on a particular topic. Readers should consult the website for the full list of responses and any authors' replies, which usually arrive after our selection.

EUGENE HOSHIKO/PA

OSELTAMIVIR'S ADVERSE REACTIONS

Fifty sudden deaths may be related to central suppression

In his editorial on the association between oseltamivir phosphate (Tamiflu or oseltamivir-P) and neuropsychiatric disturbance in adolescents Maxwell says that the case is not proved but caution is advisable.[1] On 16 June 2007 the Japanese Ministry of Health Labour and Welfare announced that by 31 May 2007 it had received 1377 reports of adverse reactions since 2001, when marketing of oseltamivir started in Japan.[2]

Of these, 567 were serious neuropsychiatric cases, 211 showing abnormal behaviour. The number of deaths reported was 71. These are not only "adverse events" but also "adverse reactions" to oseltamivir because many doctors classed and reported them as probably related or that causality could not be ruled out. However, the ministry classed all but four as "rather negative," believing that the four were allergic in origin.

In addition to these 71 deaths, there were nine sudden deaths which the ministry did not recognise as adverse reactions.

Of the total 80 deaths, 50 were sudden deaths or deaths from sudden cardiopulmonary arrest (18 in those <10 years old, 32 in those aged 20 or over), while eight were accidental deaths from abnormal behaviour (five in teenagers, three in those aged 20 or over). All 58 deaths were classed as "rather negative" by the ministry—totally different from many doctors' classifications. Four deaths were from sepsis following pneumonia after possible respiratory suppression, 10 were possibly related to exacerbation of mainly pneumonia, and eight were from hepatic failure, pancytopenia, gastrointestinal bleeding, etc.

Thus adverse reactions to oseltamivir may be roughly classified into three groups: (*a*) sudden onset reactions related to central suppressive action of oseltamivir-P during cytokine storm, including sudden death, abnormal behaviours, and other sudden neuropsychiatric disorders[3 4]; (*b*) late onset reactions such as pneumonia, sepsis, hyperglycaemia, and late onset neuropsychiatric disorders possibly related to inhibition of human cytosolic neuraminidase (sialidase) activity by oseltamivir carboxylate[5]; and (*c*) allergic reactions and others.

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1 Maxwell C. Tamiflu and neuropsychiatric disturbance in adolescents. *BMJ* 2007;334:1232-3. (16 June.)
2 Advisory Committee on Drug and Food. Second annual meeting of the Sub-Committee on Safety of Medicine for 2007 held on 16 June 2007 www.mhlw.go.jp/shingi/2007/06/s0616-1.html (in Japanese)
3 Hama R. New type of influenza-related encephalopathy or new adverse drug reaction? www.bmj.com/cgi/eletters/328/7433/227#98374
4 Hama R. Limited benefit and potential harm of oseltamivir including sudden death and death from abnormal behaviour. www.bmj.com/cgi/eletters/331/7526/1203-b#122513
5 Li CY, Yu Q, Ye ZQ, Sun Y, He Q, Li XM, et al. A nonsynonymous SNP in human cytosolic sialidase in a small Asian population results in reduced enzyme activity: potential link with severe adverse reactions to oseltamivir. *Cell Res* 2007;17:357-62.

FAFFING ABOUT

Pandemic preparedness is like house insurance

Delamothe attacks those working to address the possibility of a flu pandemic.[1] There may be rather too many international meetings, and media reports do on occasion amplify the genuine and widespread concerns of many knowledgeable scientists, but—given the general apathy, particularly in Europe—it is necessary for those of us who are preparing affordable plans to find ways to address the public. Otherwise they would have no counter to the complacency which the editorial encourages. With Fedson, I have focused particularly on how new vaccines that are already approved for seasonal flu or are close to approval could be produced in existing vaccine and biopharmaceutical protein facilities.[2] This would avoid the capital costs of billions of dollars globally to match the US current pandemic preparedness investment. However, it would require time consuming, though relatively inexpensive, negotiations on intellectual property and technology transfer. The activity has no commercial incentive, so governments would need to enable it. They will not do that if the medical establishment constantly argues it is unnecessary.

Pandemic preparedness is like house insurance: one hopes not to need it, but if a severe pandemic comes, as things stand, the total global vaccine capacity with the best adjuvant could after six months cover only 700 million of the 6400 million global population, and that will not change in the next 10 years. For the rest, the situation would be essentially the same as in 1918 because antibiotics do not seem to be of great importance. Delamothe may be happy to have that on his conscience, I am not.

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1 Delamothe T. Editor's choice: FAFfing about. *BMJ* 2007;334. (30 June.)
2 Fedson DS, Dunnill P. New approaches to confronting an imminent influenza pandemic. *Permanente Journal* 2007;11:63-9.

Evaluating pandemic risk

Delamothe asks why we should be any more worried about pandemic flu in 2007 than in 1997 or 2017.[1] There are certain observable biological events (such as repeated human infections by a novel avian virus) that are potential precursors to a pandemic and may give us some warning of what might be imminent, a luxury that previous generations did not have. To the extent that advances in virology and epidemiology have made it possible for us to document such changes in the behaviour of viruses, it would be foolish, indeed irresponsible, for us to not make use of the information available.

This is exactly the same as how one would use weather forecasts or flood or hurricane warnings to inform one's behaviour. With regard to H5N1, I would submit that we are in the same position as New Orleans was 24 hours before Hurricane Katrina hit: we can't be sure we are going to get a direct hit, but it

would be prudent to assume the worst and make preparations accordingly.

Delamothe next asks whether those responsible for planning for the next pandemic could do their planning less publicly and put the frighteners on the rest of us only at the appropriate time. In his foreword to a booklet compiled by a community of volunteers, David Heymann, executive director of Communicable Diseases, World Health Organization, says

Public health authorities throughout the world agree that the responsibility to respond to a public health emergency such as pandemic influenza cannot be fully placed under the responsibility of health workers and other primary responders, who may themselves become incapacitated by illness and death. It is thus each individual's responsibility, alone or collectively, to plan for and respond to a pandemic in the home and/or in the community.[2]

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1 Delamothe T. Editor's choice: FAFfing about. *BMJ* 2007;334. (30 June.)
2 Mid-Peninsula Citizen's Preparedness Committee. Influenza pandemic preparation and response: a citizen's guide. www.newfluwiki2.com/upload/Citizen's%20Guide%20-%20Version%201.2.pdf.

HIV

HIV exceptionalism must end

The need for HIV policy reform has again been highlighted,[1] reinforcing earlier claims that HIV testing should not have special status as knowledge about HIV status can be lifesaving.[2] Such opinions are seemingly ignored by the UK government and medical establishment, whereas in the United States reform is under way.

Last week's *BMJ* featured the cases of two apparently healthy babies who presented later with established HIV. The mothers' infection had escaped detection.[3] Abolishing exceptionalism would prevent such failure by restoring named feedback. Few mothers realise the importance of this information; namely, the drastic consequences of withholding positive results. Full understanding usually arouses incredulity and anger.[4]

Reform must come soon—litigation costs, stigma, and fear of exposure are probably stemming a tide of legal questioning among relatives unnecessarily bereaved by late HIV diagnosis.

Such trouble was predicted in 1998,[5] yet nine years of General Medical Council and BMA inaction have passed since this well argued case to progress "from exceptionalism to normalisation."

Less well known is a high court judgment ruling that an infant's human rights to HIV testing outweigh parental rights of choice. Another court could soon find that the right to be born free of HIV infection outweighs all other considerations.

Doctors and politicians failing to take note do so at their future peril. Waiting for cost effectiveness evidence is unethical.

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4 De Zulueta P. The ethics of anonymizing HIV testing of pregnant women: a reappraisal. *J Med Ethics* 2000;26:16-21.
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The societal costs of failing to develop a vaccine

Policymakers should consider not the cost of developing a vaccine against HIV, but the cost to society if it fails to develop one.[1]

In the developed world, some patients on antiretroviral treatment will develop drug resistance and the number will be cumulative each year. Medical care costs will increase exponentially for drug resistant patients, greatly exceeding the price of treatments.

Primary HIV-1 drug resistance ranges from 6.6% in Brazil to 10% in Spain to 27.7% in North America,[2] perhaps because of more frequent testing in developed countries.

Yet, this may be a portent of what will come in the developing world. By the end of this year, two million people will probably be on AIDS treatment. Many come from resource limited settings, where initial testing is limited, adherence is problematic, and substandard drugs are used as first line treatment. Suboptimal adherence is the most important factor in virological failure. Adherence is low in resource limited settings, increasing the possibility of early onset of drug resistance.

If the rate of resistance in the developing world is around 10% then 200 000 people would be drug resistant by 2010 and would move on to second line therapies. Second line treatments are over 20 times as expensive as first line ones,[3] and patients on such treatments need care from skilled and relatively well paid medical professionals.

Failing to focus on developing an AIDS vaccine will lead to a sequential increase in the number of chronically sick people whose care and maintenance will prove financially unsustainable for donors and affected governments.

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2 Debrework Zewdie, et al. *AIDS: resistance and adherence*. Vol 18, suppl 3. Washington, DC: World Bank, 2004.
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FINANCIAL INCENTIVES AND GPS

What about the impact on patient health?

McDonald et al's report of general practitioners' and nurses' views of the quality and outcomes framework (QOF) highlights the "box ticking" nature of this pay-for-performance contract.[1] We have therefore proposed that incentives are linked more directly to positive health outcomes.

Rotherham practices achieved highly on the smoking related QOF indicators in 2005 and 2006, costing the primary care trust (PCT) about £276 000 in 2005 and £500 000 in 2006. But the smoking prevalence among those on Rotherham's QOF chronic disease registers remained unchanged.

We have proposed to the PCT executive and the local medical committee that the QOF contract be renegotiated. We suggested for the smoking related indicators that the four week quit target set for us as a PCT is allocated proportionally between practices; then, at year end, practices are rewarded a proportion of the 68 QOF points allocated for the current smoking indicators according to the number of quitters relative to their target.

Moving away from tick box based incentives towards outcome based incentives could seem to be penalising GPs for their patients' unhealthy behaviours. However, as a PCT, we are responsible for the health of our population, and we believe that this is a sentiment shared by our GPs. We are held accountable as a PCT through the quit target for decisions made by our population, an accountability it seems only fair to share.

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1 McDonald R, Harrison S, Checkland K, Campbell SM, Roland M. Impact of financial incentives on clinical autonomy and internal motivation in primary care: ethnographic study. *BMJ* 2007;334:1357-9. (30 June.)