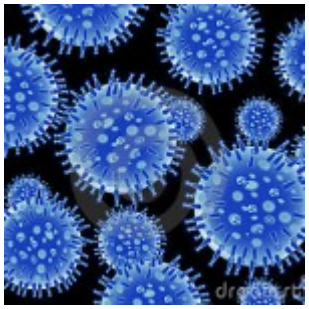
Antiviral stockpiles for pandemic preparedness: Time for a careful rethink?

11 May 2014

Nick Wilson, Michael Baker

As part of influenza pandemic readiness, NZ has a 32 million dollar stockpile of antiviral drugs. But given recent evidence from a new Cochrane systematic review – NZ policymakers should probably now carefully review this approach.



This blog discusses some of the new evidence and suggests options for a review process.New Zealand seems to have done a fairly good job of influenza pandemic planning as per a previous review just before the 2009 pandemic. This planning may have contributed to some of the favourable features of the health sector response to this 2009 pandemic (reviewed here in the *NZ Medical Journal*) – albeit a relatively mild pandemic compared to previous ones. Part of the NZ Ministry of Health's current planning includes stockpiling of antivirals. This stockpile includes more than one million doses of oseltamivir (*Tamiflu*) and 300,000 of zanamivir (*Relenza*), costing $32 million.

What is new (and recently covered in the media) is the evidence from a recent Cochrane systematic review around the effectiveness of these antivirals. This review benefited from the inclusion (after a long process of requesting them) of "107 clinical study reports from the European Medicines Agency (EMA), GlaxoSmithKline and Roche".

The review reported a fairly modest benefit from the treatment of adults, "oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours". Also "zanamivir reduced the time to first alleviation of symptoms in adults by 0.60 days". But in terms of hospitalisations, the treatment of adults with oseltamivir had no significant effect on hospitalisations and zanamivir hospitalisation data were unreported. Furthermore, the Cochrane review authors documented the relative harm from antivirals eg, "the use of

oseltamivir increases the risk of adverse effects, such as nausea, vomiting, psychiatric effects and renal events in adults and vomiting in children…".

The Cochrane reviewers also noted that there were many limitations with the trials they reviewed: "Inadequate reporting put most of the zanamivir studies and half of the oseltamivir studies at a high risk of selection bias."…. "Attrition bias was high across the oseltamivir studies and there was also evidence of selective reporting for both the zanamivir and oseltamivir studies. The placebo interventions in both sets of trials may have contained active substances." Furthermore there were inadequate measures in place to protect 11 studies of oseltamivir from bias due to "non-identical presentation of placebo".

Debate about the findings of this review and other evidence for and against antivirals being worthwhile have been included in the last two issues of the *British Medical Journal* – and might continue for some time yet. There is also discussion about the story of anti-influenza drugs being one of "multisystem failure" with trial data held by drug companies not being made publicly available. Indeed, a NZ Cochrane fellow, Dr Vanessa Jordan, was recently on NZ radio saying that the release of data held by drug companies shows that Tamiflu and Relenza are largely ineffective and governments should insist on seeing all clinical trial data before buying drugs to avoid being hoodwinked again.

But what should NZ policy-makers do now?

Until we have a highly effective universal vaccine for all influenza subtypes, there will be continuing pressure to stockpile pharmaceuticals that offer hope of protecting individuals against new pandemic influenza viruses (and for treating them), particularly for health care workers and other vulnerable groups. As much as possible, such 'hope' needs to be evidence-based, and revised as new knowledge becomes available.

So given the large cost of the antiviral stockpile to the NZ taxpayer and the need for the public and health workers to have confidence in any antiviral stockpile, it is probably desirable that NZ health authorities conduct a thorough and transparent review of the evidence around the use of antivirals for influenza prophylaxis and treatment. This review could address the following issues:

- What information besides the new Cochrane systematic review needs to be considered (eg, this systematic review of observational studies suggestive of

benefit from antivirals; and this systematic review recently published in *Lancet Respiratory Medicine* indicating a mortality reduction benefit for hospitalised patients).

- What is the evidence around the practicalities of using antivirals during a pandemic for prophylaxis and also for treatment? For example, one article on the UK experience in 2009 suggested that antivirals were of no practical benefit for prophylaxis in the community.
- What is the evidence around likely cost-effectiveness eg, cost-per-illness prevented (eg, in an emergency worker during a pandemic) and cost-per-hospitalised patient prevented from dying? New economic modelling work might be required to answer such questions (since former modelling that included consideration of the cost-effectiveness of NZ doing stockpiling might now be outdated).
- How do any of the above cost-effectiveness estimates compare with other ways to reduce spread of an influenza pandemic (eg, mass media campaigns around improving hygiene and promoting staying at home when sick)? Or how might it compare with enhancing hospital surge capacity? Our own work based on the 2009 pandemic does suggest "that hospital care was likely to be a relatively cost-effective means of preventing death from pandemic influenza".
- If antivirals are ultimately thought to have a worthwhile role in pandemic control and reducing burden on the health system – then what is the best approach to obtaining them? Is it to continue to have a national stockpile (with the inherent waste when expired product has to be thrown out), or is it more cost-effective to have a contract and annual fee payment to manufacturers for guaranteed immediate supply (as per "manufacturer reserve programmes")? The issues are quite complex as per this economic modelling study.

Finally, NZ policy-makers might wish to take this opportunity to consider further upgrades to pandemic planning. In particular, it would be good to see modelling work that assessed the scope for imposing temporary restrictions at national borders and internal borders (eg, between the North and South Islands and offshore islands). New Zealand's border screening used in the 2009 influenza pandemic appeared to have been relatively ineffective, so improving these processes should be a key priority. Such control could buy time to prepare better or reduce peak effects during an influenza pandemic (and reduce the risk of health services being overwhelmed). Such planning could also inform responses to other pandemic agents – including any future genetically-engineered bioweapons.

Public Health Expert Briefing (ISSN 2816-1203)
