Using a small stockpile of a secondary antiviral drug in a flu pandemic

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In a global influenza pandemic, small stockpiles of a secondary flu medication - if used early in local outbreaks - could extend the effectiveness of primary drug stockpiles, according to research made available today ahead of publication in *PLoS Medicine*.

Many countries are investing in large stockpiles of a single drug, oseltamivir (Tamiflu). But influenza viruses can become resistant to antiviral drugs, and the widespread use of a single drug is likely to increase the risk that a resistant strain will emerge. If such a strain were to spread widely, the effectiveness of antiviral drugs in treating infected patients, as well as their ability to slow the spread of a pandemic, would be greatly reduced.

Using a mathematical model to represent the global spread of pandemic influenza, an international team of researchers led by Joseph Wu of the University of Hong Kong, and including collaborators in the UK and the US, found that treating as few as only the first 1% of the population in a local epidemic with a secondary drug rather than with oseltamivir, could substantially delay the development of resistance to oseltamivir. This reduction in resistance was predicted to benefit not only local populations, but also those in distant parts of the world where the pandemic would subsequently spread through air travel.

In the context of the currently emerging swine flu, the secondary drug could be zanamivir (Relenza), the only other approved drug to which the new H1N1 strain has been found to be susceptible.

This strategy is predicted to be effective because it delays use of the primary stockpiled drug until a certain proportion of the local population (about 1.5% according to the model) has been infected with virus that remains susceptible to the primary drug. With drug-sensitive virus in the majority as people recover from infection and develop immunity, only a minority of further infections are likely to be resistant to the primary drug.

Technically, such a delay could be achieved by postponing the launch of any antiviral intervention. However, because even a short delay would mean denying antiviral drugs to people who would benefit from them, the researchers instead propose the deployment of a small stockpile of a secondary antiviral during the early phase of the local epidemic.

The model, prepared before the current swine flu crisis, considered two possible strategies, "early combination chemotherapy" (treatment with two drugs together while both are available, assuming that clinical trials show such a combination to be safe for patients) and "sequential multi-drug chemotherapy" (treatment with the secondary drug until its stockpile is exhausted, then treatment with the primary drug). While either strategy could be effective in principle, only the sequential strategy would be practical in responding to the currently emerging H1N1 swine flu, because the safety of combining zanamivir with oseltamivir (for combination therapy) is not established.

After simulating the impact of these strategies in a single population, the researchers then introduced international travel data into their model to investigate whether these two strategies could limit the development of antiviral resistance at a global scale. This analysis predicted that, provided the population that was the main source of resistant strains used one of the strategies, both strategies in distant, subsequently affected populations would be able to reduce the consequences of resistance, even if some intermediate populations failed to control resistance.