The Global Spread of Drug-Resistant Influenza

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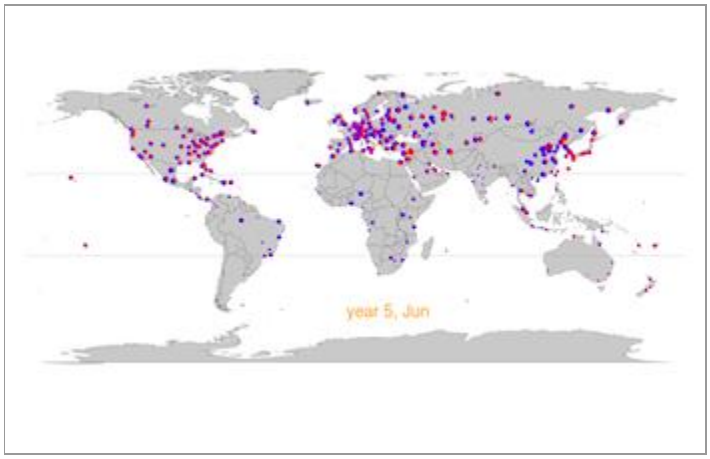
Antiviral drugs such as oseltamivir (Tamiflu) are used for treatment and prophylaxis of both highly pathogenic influenza and seasonal influenza, especially for those in high-risk groups. While mutations in flu strains might confer resistance to oseltamivir, it had previously been believed that none of these mutations were of clinical significance, affecting seasonal H1N1 strains from 1999 and earlier. However, one specific mutation, H274Y, went to fixation (becoming the only possible phenotype) very rapidly between 2006 and 2009. The speed with which oseltamivir resistance spread was very perplexing, given that the drug's overall global usage has been low. To better understand how the rapid global spread of H1N1 could occur, Dr. Dennis Chao and colleagues at the Center for Statistics and Quantitative Infectious Diseases, a division of the Vaccine and Infectious Disease Division (VIDD), developed a stochastic model of the global transmission of influenza.

In the model system, oseltamivir-sensitive and resistant influenza can infect people in 321 cities connected by air travel. This model tests how oseltamivir-resistant strains would spread relative to their sensitive counterparts, and how the usage of the drug could increase the prevalence of drug-resistant influenza. Using this well developed model, the group found that a drug-resistant virus would be unable to establish itself, even if only slightly less transmissible than the sensitive virus. This explains the lack of resistance in H1N1 in the 1990s, though by 2007 seasonal H1N1 had acquired mutations that eliminated the fitness difference between sensitive and resistant strains. The model analysis showed that mutations that increased transmissibility in untreated individuals were associated with the most rapid increases in drug resistant H1N1.

These findings have implications for predicting the spread of resistance in the 2009 pandemic influenza. Increased infection control for treated individuals may slow the spread of drug-resistant strains of influenza by delaying the establishment of resistant strains in the global population. Importantly, these results show that resistant pandemic H1N1 might be slightly reduced in transmissibility, and the resistant virus would not continue to spread if it is less transmissible than the oseltamivir-sensitive counterpart.

Chao DL, Bloom JD, Kochin BF, Antia R, Longini IM. 2011. The global spread of drug-resistant influenza. *Journal of the Royal Society Interface.* doi: 10.1098/rsif.2011.0427



A model of global influenza transmission. Dot sizes are proportional to population, representing 321 cities.