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Pandemic influenza A(H1N1)v viruses currently circulating in New Zealand are sensitive to oseltamivir

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New Zealand, like other southern hemisphere countries with a temperate climate, has been in the winter period with seasonal influenza activity. New Zealand has also experienced a dramatic increase in the number of cases of pandemic influenza A(H1N1)v virus. Early reports from the northern hemisphere at the beginning of the pandemic showed that the virus was sensitive to the antiviral drug oseltamivir. In this study we report that pandemic influenza A(H1N1)v viruses currently circulating in New Zealand are sensitive to oseltamivir, but seasonal influenza A(H1N1) viruses – the co-circulating predominant seasonal strain, is resistant to oseltamivir.

Since the declaration of a pandemic by the World Health Organisation on 12 June 2009, New Zealand has seen a surge in the number of cases of pandemic influenza A(H1N1)v. As of 16 July 2009, there have been 2,107 laboratory-confirmed cases in New Zealand and 10 deaths; the actual number of infections is certainly much higher. Like other southern hemisphere countries with a temperate climate, New Zealand entered the winter period with seasonal influenza activity. The national influenza surveillance system detected co-circulation of pandemic A(H1N1)v virus and seasonal influenza strains. Infection with pandemic A(H1N1)v has rapidly outnumbered seasonal influenza viruses within just a month [1].

The current recommended antiviral drug for treatment of pandemic A(H1N1)v is the neuraminidase inhibitor oseltamivir (Tamiflu®). Oseltamivir has been used in New Zealand to limit entry and spread of the virus since an initial incursion on 26 April 2009, for the treatment of quarantined cases and as prophylaxis for close contacts during the containment phase, and now mainly for the treatment of cases during the management phase.

Surveillance for oseltamivir-resistance in pandemic A(H1N1)v viruses currently present in New Zealand was undertaken using a fluorometric neuraminidase inhibition assay on cultured viral isolates (n = 20) from MDCK and MDCK-SIAT1 cells [2,3]. This assay determines neuraminidase activity using a fluorogenic substrate in the presence of increasing concentrations of oseltamivir. The 50% inhibitory concentration (IC₅₀) is the value at which neuraminidase activity is inhibited by 50%. All pandemic A(H1N1)v viruses were identified as being susceptible to oseltamivir, with IC₅₀ values ranging from 0.183 nM to 0.745 nM (Table). Sequencing of the neuraminidase gene of 10 viruses showed that none harboured the H275Y mutation (N1 numbering) that is known to confer oseltamivir-resistance. Sequencing of the M2 (matrix) protein from four of the cultured isolates showed that these viruses contain the S31N mutation in the M2 protein that confers resistance to the adamantane class of anti-influenza drugs. This data are in agreement with previously published findings on antiviral drug resistance for pandemic A(H1N1)v viruses [4]. In conjunction, oseltamivir-resistance in the predominant seasonal influenza A(H1N1) that is co-

circulating with pandemic A(H1N1)v in 2009 was determined. Seasonal A(H1N1) viruses (n = 24) showed 100% incidence of oseltamivir-resistance with IC50 values ranging from 305 nM to 7912 nM (Table). This represents a 1,400-fold increase from the mean IC50 = 0.94 nM detected for previous oseltamivir-sensitive viruses in New Zealand from before 2008 (unpublished data). Sequencing of the neuraminidase gene (n = 10), and restriction fragment length polymorphism analysis [5] (n = 28) in seasonal A(H1N1) viruses revealed that viruses contain the H275Y mutation (N1 numbering) and share a high level of sequence identity with other seasonal A(H1N1) oseltamivir-resistant viruses that were first detected in Norway in January 2008 [6].

Table. Sensitivity to oseltamivir (Tamiflu) of influenza viruses isolated in New Zealand from January to July 2009

These data show that the use of oseltamivir will be effective for the treatment of pandemic A(H1N1)v infection, but will not be effective for the treatment of seasonal A(H1N1). Surveillance for oseltamivir-resistance in pandemic A(H1N1)v is important given that oseltamivir is one of the few pharmacological interventions available before an effective pandemic vaccine becomes widely available. In addition, the presence of oseltamivir-resistant seasonal A(H1N1) viruses co-circulating in the community demonstrates that influenza can be resistant to neuraminidase inhibitors without any apparent compromise in fitness or transmissibility. Close monitoring of antiviral susceptibility of pandemic A(H1N1)v is of increasing importance given the three recent isolated cases from Denmark, Japan and Hong Kong which are oseltamivir-resistant [7]. Furthermore, New Zealand faces a unique challenge where the oseltamivir-resistant seasonal A(H1N1) strain and oseltamivir-sensitive pandemic A(H1N1)v are co-circulating in the community, thus having the potential for re-assortment.

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