

EMERGENCE OF RESISTANCE TO OSELTAMIVIR AMONG INFLUENZA A(H1N1) VIRUSES IN EUROPE

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Surveillance of the antiviral susceptibility of influenza viruses circulating in Europe has been established since 2004 through the European Union-funded European Surveillance Network for Vigilance against Viral Resistance (VIRGIL), in collaboration with the European Influenza Surveillance Scheme (EISS), the World Health Organization (WHO) and national influenza centres. Results from analysis of early winter (November 2007 – January 2008) A(H1N1) virus isolates has revealed that a significant proportion, approximately 14% of these European strains (see Table), are resistant to oseltamivir (Tamiflu), the most widely used anti-influenza drug, but retain sensitivity to zanamivir (Relenza) and amantadine/rimantadine.

As of week 03/2008, 16 European countries have reported significant influenza activity (Austria, Belgium, Bulgaria, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Northern Ireland, Poland, Portugal, Romania, Slovenia, Spain and Switzerland). Of the total virus detections since week 40/2007 (N=3447), 81% have been influenza A and 19% influenza B, and the predominant viruses circulating in most countries have been A(H1N1) similar to the A/Solomon Islands/3/2007 vaccine strain [1]. The presence of oseltamivir-resistant viruses circulating in the community in several European countries (Denmark, Finland, France, Germany, Netherlands, Norway, Portugal, Sweden and United Kingdom) is in marked contrast to the previous winter seasons of 2004/2005, 2005/2006, and 2006/2007, when oseltamivir resistance was detected in <1% of circulating strains from 24 countries.

A total of 437 influenza A(H1N1) viruses, isolated between November 2007 and January 2008, were tested using measurement of neuraminidase (NA) enzyme activity in the presence of oseltamivir to determine the drug-sensitivity (IC50) of the viral enzyme (2) in conjunction with sequence analysis of the viral neuraminidase gene. To date, oseltamivir-resistant viruses have been detected in nine countries (Table 1); in particular, 26 of 37 (70%) in Norway, 15 of 87(17%) in France, 3 of 43 (7.0%) in Germany and 8 of 162(5%) in the United Kingdom carry the same mutation, causing the substitution of histidine by tyrosine at residue 274 (H274Y) of the neuraminidase, which is known to confer a high level resistance to oseltamivir. Viruses bearing this mutation, when tested in enzyme assays, showed a reduction of approximately 400 fold in susceptibility to oseltamivir (IC50 values increased from approximately 1nM to more than 400nM). All these viruses remain sensitive to the other anti-neuraminidase drug zanamivir and to the anti-M2 drugs amantadine and rimantadine.

The resistant (H274Y) viruses have been isolated from both adults and children, ranging from 1 month to 61 years in age, with the majority of viruses being isolated from adults. So far, there is no information that any of these viruses, in any country, has been obtained from a person who has either been treated or been in close contact with another individual who has been treated with oseltamivir. We therefore conclude that the identification of these oseltamivir-resistant viruses as a substantial proportion of circulating viruses, particularly in Norway, is the first clear evidence that influenza A(H1N1) virus with the H274Y mutation can readily transmit between individuals.

TABLE 1

A(H1N1) viruses resistant to Oseltamivir in Europe, winter season 07/08 (Nov 2007-Jan 2008)

Country	Total tested	Oseltamivir resistant by IC50(nM) or by 274Y	Percentage resistance with 95% confidence intervals
Austria	5	0	0% (0-43 %)
Denmark	10	1	10% (2-40%)
Finland	7	2	29% (8-64%)
France	87	15	17% (11-27%)
Germany	43	3	7% (2-19%)
Greece	5	0	0% (0-43%)
Hungary	5	0	0% (0-43%)
Italy	13	0	0% (0-23%)
Latvia	4	0	0% (0-49%)
Netherlands	16	1	6% (1-28%)
Norway	37	26	70% (54-83%)
Portugal	6	2	33% (10-70%)
Slovakia	5	0	0% (0-43%)
Slovenia	1	0	0% (0-79%)
Spain	11	0	0% (0-26%)
Sweden	13	1	8% (1-33%)
Switzerland	7	0	0% (0-35%)
United Kingdom	162	8	6% (3-9%)
Total	437	59	14% (11-17%)

More extensive surveillance within Europe and in other parts of the world is required to establish the relative prevalence and geographical distribution of these resistant viruses, and to evaluate their potential impact on the effectiveness of drug use. The spectrum of clinical illness associated with infection by oseltamivir-resistant viruses remains to be fully determined, although limited information from initial clinical cases does not suggest unusual disease syndromes. Although the resistant viruses have been isolated from November through January, the ability of these viruses to persist throughout the influenza season, and from one season to the next, will require continuous world-wide surveillance by the WHO Global Influenza Surveillance Network. Determining the origins and genesis of these drug-resistant strains, which appear to have emerged in regions of the world where there is little drug pressure, will be important in understanding the emergence and persistence of oseltamivir resistance in relation to the evolution of influenza viruses and drug use.

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