

OBSERVED OSELTAMIVIR RESISTANCE IN SEASONAL INFLUENZA VIRUSES IN EUROPE INTERPRETATION AND POTENTIAL IMPLICATIONS

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In this week's issue of *Eurosurveillance*, Zambon and colleagues describe the first findings of the European Union-funded European Surveillance Network for Vigilance Against Viral Resistance (VIRGIL) of some seasonal influenza viral isolates resistant to the antiviral drug oseltamivir in Europe [1]. Since the winter of 2004-5, a sample of influenza viral isolates have been routinely monitored by VIRGIL for antiviral resistance in a number of EU member states and other European countries [2]. Testing of the isolates for the 2007-8 season began in late January, with the finding that in the specimens for the first 10 countries, four countries had a proportion of seasonal influenza A/H1N1 with a mutation that confers a high level of resistance to the drug oseltamivir. The proportion of A/H1N1 isolates that were resistant was especially high in Norway [1], both in genome sequencing and phenotypical testing.

An interim risk assessment was published by the European Centre for Disease Prevention and Control (ECDC) on 27 January based on these preliminary findings and the available science [3]. As of January 31, resistant isolates have been found in nine out of 18 of the European countries whose specimens were tested (Denmark, Finland, France, Germany, the Netherlands, Norway, Portugal, Sweden and the United Kingdom (UK)) [1]. Although a high proportion of isolates have been found resistant (overall figure of approximately 14%), the sample size was relatively small, meaning this may not accurately reflect the proportion that are resistant among all infections. Norway and VIRGIL alerted the World Health Organization (WHO) and all 27 EU and the other two EEA countries (Iceland and Liechtenstein) through the International Health Regulations and Early Warning Response System. Further testing has begun in the laboratories of the Centre of Infections of the UK's Health Protection Agency as well as the WHO Influenza Collaborating Centre in London, and through sequencing and phenotypic testing in national influenza centres. The WHO has held international consultations, and testing in WHO Collaborating Centres has identified similar findings in some other parts of the world, although not all. It is not yet clear from where these viruses emerged, or why. However, as they are in Europe, we must address them. The fact that the first findings came from Europe may simply be a reflection of the surveillance methods used here and the timeliness of the work. They should not be taken to imply that they emerged in Europe. The WHO is now coordinating further investigations at a global level, while the ECDC, working with the WHO European Region and the European Commission, is coordinating investigations in the EU and EEA/EFTA countries.

The oseltamivir resistance investigation is still in its early stages, with a small number of samples from several countries tested. A more accurate picture will only emerge when many more specimens have been tested and more epidemiological information is available. Influenza activity this season has only recently begun to significantly increase in Europe and A/H1N1 has been the predominant strain circulating so far [4]. From the samples examined to date, the proportions of the new virus A/H1N1 with the H274Y mutation appear to be low [1].

Oseltamivir is seemingly not frequently used in Europe, although better data needs to be acquired on this and the use of other antivirals. There has been no evidence to date that any of the Norwegian patients were exposed to the drug before their infection. Therefore, the resistance is unlikely to be related to antiviral medication use in individual patients in Europe. For the same reason, these findings have fewer clinical implications for routine clinical treatment of mild influenza infections than if oseltamivir was used more widely. The ECDC's interim risk assessment also emphasised that the findings are not related to avian influenza (the similarly named A/H5N1), pandemics or pandemic preparedness. However, they are a timely reminder of the ability of influenza viruses to develop antiviral resistance and the fact that it cannot be guaranteed that any novel influenza virus emerging will be sensitive to any particular antiviral medication [5,6,7,8].

Influenza seasons in which H1N1 viruses predominate are typically associated with less severe illness and lower overall mortality than seasons in which other influenza A viruses predominate. There is currently no evidence that the mutated H1N1 strain is any more virulent than other strains of seasonal influenza (all the Norwegian patients had typical influenza illnesses), but any influenza A can nevertheless cause severe disease or be fatal for vulnerable people, including infants, the elderly and those with chronic debilitating disease.

The circulating A/H1N1 viruses, including the oseltamivir-resistant ones, are well matched with the current seasonal influenza vaccine, meaning that those who have been vaccinated are already at a lower risk of contracting the disease or developing severe complications than those who have not yet been immunised. The tests conducted so far have also shown that the mutated viruses are fully susceptible to the other currently available antiviral drugs, zanamivir and the adamantanes (amantadine and rimantadine) [1]. However, it is agreed that there is currently insufficient evidence for authorities to consider changes to clinical guidelines.

Resistant viruses carrying the same mutation have been seen in previous seasons but, as with most resistant viruses, were few in number, 'unfit' and transmitted poorly. Consequently, 'fitter' non-resistant viruses eventually predominated. The cautious use of antiviral medication may have contributed to this. These A/H1N1 isolates with the H274Y mutation are fitter. They are in several countries and are transmitting in the community [1]. The specimens tested to date are from early in the season and it may be that as the season progresses ordinary A/H1N1s predominate. Equally, the resistant viruses may come to predominate, as did the adamantane-resistant viruses in other H-types in some parts of the world, notably North America [5]. Careful virological and epidemiological surveillance should continue for the rest of this and other seasons. The ECDC will revise its assessment as more information on this issue emerges and comments are received. In collaboration with VIRGIL and the European Influenza Surveillance Scheme (EISS), the Centre will also regularly update the figures on resistance in Europe, initially on a weekly basis. More information about seasonal influenza can be found on the websites of the ECDC (<http://www.ecdc.europa.eu>) and the WHO (<http://www.who.int>).

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