

## Research articles

# USE OF OSELTAMIVIR IN 12 EUROPEAN COUNTRIES BETWEEN 2002 AND 2007 – LACK OF ASSOCIATION WITH THE APPEARANCE OF OSELTAMIVIR-RESISTANT INFLUENZA A(H1N1) VIRUSES

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Variable levels of oseltamivir resistance among seasonal influenza A(H1N1) isolates have been reported in Europe during the 2007-8 northern Hemisphere influenza season. It has been questioned whether oseltamivir use could have driven the emergence and predominance of resistant viruses. This study aimed at describing the levels of use of oseltamivir in 12 European Union (EU) Member States and European Economic Area (EEA)/European Free Trade Area (EFTA) countries. The data were converted into prescription rates and compared with the national proportions of resistant influenza A(H1N1) viruses through regression analysis. Overall use of oseltamivir in European countries between 2002 and 2007 was low compared to e.g. the use in Japan. High variability between the countries and over time was observed. In eight of the 12 countries, there was a peak of prescriptions in 2005, coinciding with concerns about a perceived threat from an influenza pandemic which might have led to personal stockpiling. Ecological comparison between national levels of use of oseltamivir in 2007 and the proportions of A(H1N1) viruses that were resistant to oseltamivir showed no statistical association. In conclusion, our results do not support the hypothesis that the emergence and persistence of these viruses in 2007-8 was related to the levels of use of oseltamivir in Europe. Further investigation is needed to elucidate the reasons for different level of use between the countries.

### Introduction

Annual epidemics of human seasonal influenza are associated with a substantial burden of morbidity and mortality, which cumulates in certain groups of the population such as older people and those with chronic medical conditions [1-3]. Annual vaccination remains the mainstay of influenza prevention, and antiviral medications, including the neuraminidase inhibitors (NAIs) oseltamivir and zanamivir, and M2 protein inhibitors (the adamantanes amantadine and rimantadine) play an auxiliary role in the prevention or treatment of influenza infection. They can be especially helpful in controlling outbreaks in nursing homes, in individuals who cannot be immunised or in situations in which vaccine has not been given or in which vaccination is not optimally effective due to a poor match between the vaccine strain and the circulating strains [4-9].

NAIs, especially the oral drug oseltamivir, became increasingly important after a sudden increase in adamantane resistance among seasonal influenza A viruses between 2004 and 2006 [5,10,11]. NAIs have also been preferred in recommendations to amantadine (the most commonly used adamantane) since they show lower levels of adverse neurotoxic reactions [12]. Before the 2007-8 influenza season, resistance to the NAIs among transmitting seasonal influenza A viruses was extremely rare in Europe and elsewhere [13-15] and higher proportions of resistance had been reported only in children: up to 18% of children infected with influenza A(H3N2) and treated with oseltamivir shed virus resistant to oseltamivir [16-17]. However, NAI-resistant viruses detected before 2007-8 showed in most cases a poor ability to transmit from human to human.

This situation changed abruptly during the 2007-8 northern Hemisphere influenza season when influenza A(H1N1) virus isolates highly resistant to oseltamivir were detected as part of surveillance in the Europe through the networks of the European Influenza Surveillance Scheme (EISS)/European Surveillance Network for Vigilance against Viral Resistance (VIRGIL) [13,18]. Laboratory analyses showed that up to 67.4% of all influenza A(H1N1) viruses isolated from specimens collected between November 2007 and April 2008 in Europe either carried the mutation H274Y which is associated with high levels of oseltamivir resistance or tested positively in the IC50 phenotypic examination for oseltamivir resistance (Figure 1) [19]. This was the first indication that influenza A(H1N1) virus resistant to oseltamivir could readily transmit between humans.

The question arises whether current levels of oseltamivir use in European countries could have been associated with the emergence and sustained transmission of resistant influenza A(H1N1) viruses. The aim of the study was thus to describe, using all available data (including data from prescription surveys and databases), oseltamivir usage at population level in several EU Member States and EEA/EFTA countries and to determine if there was any correlation between the level of use and the observed proportions of A(H1N1) viruses that were resistant.

## Methods

We used several sources of information on oseltamivir prescriptions as a proxy measure for oseltamivir utilisation in EU Member States and EEA/EFTA countries.

### Information on oseltamivir use from a prescription survey

We used data from a continuing survey of a panel of office-based physicians in EU Member States and EEA/EFTA countries from databases maintained by Intercontinental Marketing Services (IMS) Health, an independent commercial company providing information on the use of pharmaceuticals. IMS Health attempts to achieve a high level of representativeness of their panels for the population of all physicians in the involved countries. Participating physicians are being surveyed for two consecutive workdays per quarter of a year and provide information on each patient encounter during this period. The manufacturer of oseltamivir, F. Hoffmann-La Roche Ltd., provided the European Centre for Disease Control and Prevention (ECDC) with the data from IMS Health on the numbers of oseltamivir prescriptions in Austria, Belgium, Finland, France, Germany and Greece for the years 2002 to 2007. We then converted

these data into prescription rates (number of prescriptions per 1,000 inhabitants per year) using Eurostat population data [20]. Four other countries monitored by IMS Health, the Netherlands, Portugal, Switzerland and the United Kingdom (UK), had only negligible prescription levels for oseltamivir.

### Information on oseltamivir use from population prescription databases

In Denmark and Norway, data on the number of patients having used oseltamivir at least once each year between 2002 and 2007 and between 2004 and 2007, respectively, were extracted from national, publicly available databases on redeemed prescriptions [21,22]. These numbers of prescriptions were converted into rates of redeemed prescriptions per 1,000 inhabitants per year. In both countries, data included corporate prescriptions, i.e. medicines purchased by business organisations for their employees. The data did not include any supply of antiviral medications to countries for national or corporate stockpiles.

### Quarterly prescription information

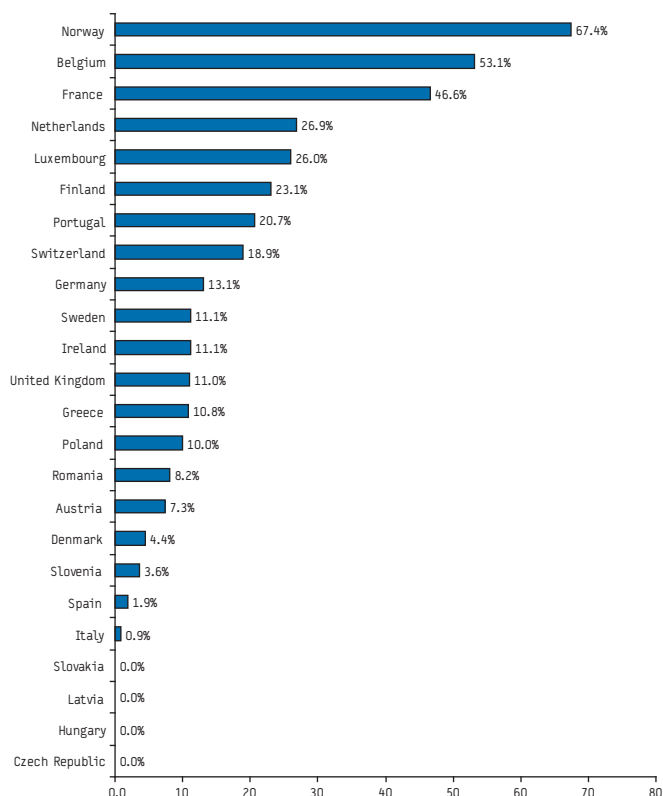
The initial analysis consisted in computing annual figures for oseltamivir prescriptions per 1,000 inhabitants. To examine trends in oseltamivir use over time in more detail, we also obtained quarterly prescription numbers and converted them into prescription rates. Quarterly data were available for eight countries: Austria, Belgium, Germany, Greece, the Netherlands, Portugal, Switzerland, and the UK.

### Investigation of the relationship between oseltamivir use and levels of resistance

Linear regression analysis was performed to determine whether there was any relationship between the use of oseltamivir and the levels of oseltamivir resistance. Proportions of oseltamivir resistance during the 2007-8 influenza season among all A(H1N1) tested strains expressed on the web sites of ECDC, EISS and the World Health Organization (WHO) were regressed on the levels of

FIGURE 1

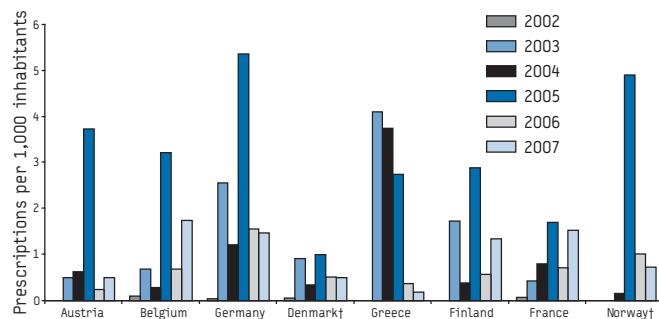
### National proportions of antiviral resistance in A(H1N1) influenza viruses for EU/EEA Member States, 2007-8



Data (available as of 6 August 2008) were provided by European Influenza Surveillance Scheme [www.eiss.org/index.cgi](http://www.eiss.org/index.cgi) and the VIRGIL Project [www.virgil-net.org](http://www.virgil-net.org). Countries with fewer than 10 test results (Bulgaria, Estonia) are not shown in the graph. EU/EEA/EFTA countries in the EISS network for which no test results were available: Cyprus, Lithuania, Malta. EU: European Union; EEA: European Economic Area EFTA: European Free Trade Area; EISS: European Influenza Surveillance Scheme; VIRGIL: European Surveillance Network for Vigilance against Viral Resistance.

FIGURE 2

### Prescriptions of oseltamivir per 1,000 inhabitants in eight European countries\*, 2002-2007



\* Data only include patient prescriptions. They do not include stockpiles at national/regional level or by hospitals/institutions. Data for Denmark and Norway include corporate prescriptions.

Netherlands, Portugal, UK and Switzerland: data not presented due to 'negligible' number of prescriptions.

† Denmark and Norway: the data are based on the number of patients, which may slightly underestimate the number of prescriptions. Source: IMS Health data provided by F. Hoffmann – La Roche Ltd., Basel except for: Denmark; data provided by Danish Medicines Agency, and Norway: data provided by Norwegian Institute of Public Health.

oseltamivir use in the countries in 2007. STATA (STATA/SE 10 for Windows, STATA Corporation) was used for statistical analyses.

## Results

### Annual oseltamivir prescription rates

As shown in Figure 2, the overall prescription rates for oseltamivir remained under six prescriptions/1,000 inhabitants/year in the eight EU Member States for which such data was available. This is low compared to those reported, for example, in Japan where the reported prescription rate in 2005 was 70.9/1,000 inhabitants/year [23].

After a substantial peak in prescriptions in 2005, when three countries exceeded three prescriptions/1,000 inhabitants/year (Austria, Belgium and Norway) and one country exceeded five prescriptions/1,000 inhabitants/year (Germany), the use of oseltamivir decreased to under two prescriptions/1,000 inhabitants/year in 2006 and 2007 in all included countries. However, the trends from 2006 to 2007 differed: an increase occurred in Austria, Belgium, Finland and France, a small decrease in Germany, Greece and Norway, and the rates remained stable in Denmark.

In the most recent year with available data (2007), we observed a substantial variation in oseltamivir prescription rates in EU Member States, with an almost tenfold differences in those countries with any significant use of oseltamivir. The highest rates were seen in Belgium and the lowest in Greece. Countries with negligible use that are not shown in the figure are the Netherlands, Portugal, Switzerland and the UK. Greece exhibited a different prescription pattern with high use in 2003 and 2004.

In summary, our analysis showed low prescription rates of oseltamivir with substantial variation between analysed countries and over time.

### Quarterly oseltamivir prescription rates

Figure 3 shows a more detailed comparison of oseltamivir prescription rates in eight countries for which data were available at the level of periods of three months.

It was noticeable that the peak of oseltamivir use observed in 2005 in Austria, Belgium, Finland and Germany (Figure 2) concentrated mostly during the first quarter of that year.

### No correlation of prescription data and resistance development

We have analysed oseltamivir resistance in 2007-8 because a sharp increase in resistance was observed during that season. We regressed it against oseltamivir use in 2007 assuming this was a good proxy for oseltamivir use in 2008. However, regression analysis for twelve countries (Figure 4) did not show any statistical association between the levels of oseltamivir resistance during the influenza season 2007-8 and oseltamivir prescriptions in 2007 ( $R^2 = 0.02$ ).

## Discussion

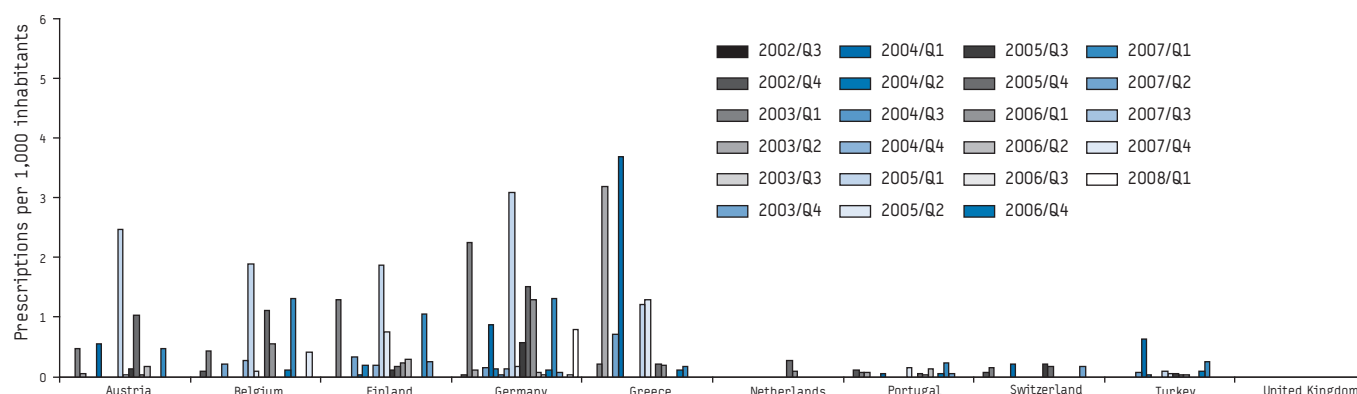
We found overall low levels of oseltamivir use in EU Member States in the period between 2002 and 2007, compared to the use of oseltamivir in Japan, a country with the world's highest per capita use of oseltamivir (70.9/1,000 inhabitants/year), but relatively low levels (3%) of oseltamivir resistance during the 2007-8 season [23,24].

There was a common peak in prescriptions in 2005 in eight countries. One possible explanation for this phenomenon is the concern over 'bird flu' influenza A(H5N1) in 2005 when spread of these viruses from Asia towards Europe received considerable attention in the media. Many of these prescriptions to individuals and families may therefore have gone to form a source of medication for the future ("personal stockpiling"). A similar spike of influenza antiviral medication sales, was observed in October 2005 in New York [25] and, in general, in the autumn and winter of 2005 across the United States [26]. It did not coincide with influenza activity itself, but rather with the beginning media coverage of avian influenza A (H5N1) and the potential for an influenza pandemic [23].

It is more difficult to explain the observation that most of the oseltamivir use in EU Member States in 2005 concentrated in the first quarter of the year. Influenza activity during the season 2004-5

**FIGURE 3**

**Prescriptions of oseltamivir per 1,000 inhabitants in eight European countries\*, 2002-2007, by quarter of a year**



Source: IMS Health data provided by F. Hoffmann – La Roche Ltd., Basel except for: Denmark; data provided by Danish Medicines Agency, and Norway: data provided by Norwegian Institute of Public Health.

only partially explains this peak. Although the media paid some attention in early 2005 to ongoing outbreaks of avian influenza among poultry in Indonesia, Thailand, and Vietnam and possibly also in Cambodia and Lao People's Democratic Republic, it was the outbreaks of avian influenza in Turkey, Romania, Croatia and the UK in October 2005 which spiked most of the media reports that year [26]. At the time there were public statements in many countries about national antiviral stockpiles being purchased by governments [28,29].

It should be noted that some countries had significant levels of prescribing even before 2005, which could be an indication for therapeutic or prophylactic application by physicians. The contrasting prescription pattern in Greece with high use in 2003 and 2004, may represent the seasonal influenza activity pattern in that country with the highest activity in February-April 2003, and then from December 2003 to the first months of 2004.

We also found a substantial variation in prescription rates between the analysed countries, which is hard to justify on any scientific grounds. Reasons may be differences in national guidelines, clinical practice patterns, marketing strategies or insurance companies' reimbursement [30]. Among the countries with negligible use of anti-influenza drugs, the UK and the Netherlands have medical guidelines on when antiviral medications are indicated that restrict their widespread use [4,12,31], while in Switzerland, most insurance companies do not reimburse the use of antivirals (D. Koch, personal communication). Exploring this phenomenon in more detail would warrant a separate study and would be justified because the wide variations in the use of antivirals for influenza does at present not reflect observed patterns of influenza-like illness/influenza and cannot be seen as having a scientific basis.

Although the analyses had to be restricted to ecological analyses, these preliminary data do not point towards any correlation between a higher prevalence of resistance and higher rates of antiviral use. Hence, it seems very unlikely that oseltamivir use has driven the rise and persistence of 'fit' oseltamivir-resistant influenza viruses

A(H1N1) in Europe in the 2007-8 season. The H274Y point mutation, which confers oseltamivir resistance is most likely a random event, and potential factors influencing its occurrence are not known [32].

Our study had several limitations, apart from being restricted to an ecological level of analysis. Firstly, we obtained information on antiviral medication prescriptions which do not necessarily represent all medications consumed. Indeed, it is possible that some of the purchased medications were not consumed but stored in "private stockpiles". This seems especially likely for the antivirals acquired in the peak year of 2005. Secondly, the IMS Health data are based on a sample of physicians who may not necessarily be representative for all physicians in the analysed countries. Thirdly, data were only available for a limited number of EU Member States and EEA/EFTA countries, and the situation could be quite different in the countries that we could not study. Moreover, for several countries we only had data on oseltamivir resistance for the first quarter of 2008.

### Conclusion

While the precise relationship between oseltamivir use and resistance of influenza A(H1N1) to oseltamivir remains uncertain, the available data do not suggest a link between the rapid rise in the proportion of the resistant A(H1N1) and the use of oseltamivir in Europe.

The use of influenza antiviral medication in EU Member States should be closely monitored in the future. More studies are needed to assess how the influenza prescription rates reflect the actual use of the medication by patients, in order to explore the potential causes of the large variation in the number of prescriptions in EU Member States and EEA/EFTA countries. In addition, a scientific discussion is needed about what are the right indicators for use of these drugs. Virological studies are needed to better understand the mechanism behind the development of oseltamivir resistance among A(H1N1) seasonal influenza viruses, and to monitor the possible emergence and spread among other influenza viruses. Epidemiological studies are needed to understand the determinants of resistance development, in order to be able to design targeted interventions and to assess the impact on transmission and clinical outcome.

### Acknowledgements

We wish to thank David Reddy and James Smith (F.Hoffmann-La Roche Ltd) for making available the data on oseltamivir use in the analysed countries.

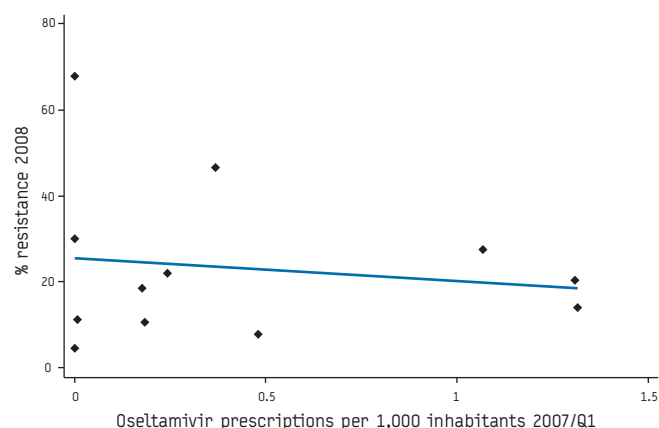
ECDC would like to thank all countries, virologists, clinicians and others for contributing data. Funding for the VIRGIL project comes from the European Union FP6 Research Programme [http://ec.europa.eu/research/health/influenza/proj13\\_en.html](http://ec.europa.eu/research/health/influenza/proj13_en.html) and EISS is supported by ECDC. Laboratories in EISS contribute to the Global Influenza Surveillance Network managed by WHO.

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**FIGURE 4**

**Regression of the proportion of resistant strains on the number of prescriptions of oseltamivir per 1,000 inhabitants in European countries**



Source as in Figure 3.

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This article was published on 5 February 2009.

Citation style for this article: Kramarz P, Monnet D, Nicoll A, Yilmaz C, Ciancio B. Use of oseltamivir in 12 European countries between 2002 and 2007 – lack of association with the appearance of oseltamivir-resistant influenza A(H1N1) viruses. *Euro Surveill*. 2009;14(5):pii=19112. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19112>