



RAPID RISK ASSESSMENT

Oseltamivir-resistant influenza A(H1N1)2009 cluster in Australia

September 2011

Conclusions and recommendations

Australia has reported a cluster of oseltamivir-resistant influenza A(H1N1)2009 cases in the state of New South Wales. The cases had no known link to oseltamivir exposure and individuals were not immunosuppressed, but they were closely linked geographically. Samples from the cluster do not currently exhibit any resistance to zanamivir.

Although the cluster has remained localised, it cannot be assumed that the variant virus will not spread. At present, the risk of this cluster becoming more widespread and having public health implications remains low.

However, if spread does occur, implications for the treatment of influenza patients will need to be considered. Regardless of the outcome, constant antiviral resistance monitoring is vital in Europe and globally.

Since the A(H1N1)2009 virus antigen is included in the recommended seasonal flu vaccine for the coming season this potential for emergence of oseltamivir resistance is yet another reason why EU citizens, for whom vaccination is recommended by Member States, should accept the offer.

Source and date of request

Internal ECDC decision, 31 August 2011.

Public health issue

Documented oseltamivir resistance of A(H1N1)2009 influenza virus in Australia, with assumed person-to-person transmission of the resistant strain.

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Disease background information

Vaccination, supplemented by personal hygiene measures, remains the primary measure for prevention of seasonal influenza transmission. However, antiviral drugs are important countermeasures for prophylaxis and treatment, especially in vulnerable people and those with severe influenza. Between 1999 and 2002, the influenza virus neuraminidase inhibitors (NAI), oseltamivir and zanamivir, were introduced into clinical practice in many parts of the world (1). Until 2007, NAI resistance was rarely observed (1). Widespread high-level resistance to oseltamivir was detected among the former seasonal A(H1N1) viruses in the 2007–2008 season, first in Norway and then in most other EU/EEA countries. The overall level of A(H1N1) resistance was 16% for Europe in the 2007–2008 season. This rose to almost 100% for A(H1N1) viruses in the subsequent southern hemisphere influenza season, and elsewhere in the world during the 2008–2009 season (2). This rise was apparently not driven by use of oseltamivir. All the resistant A(H1N1) viruses were found to carry a point mutation in their neuraminidase genes which encoded a histidine to tyrosine substitution at residue 275 (H275Y) of the neuraminidase protein (3).

Despite intensive antiviral resistance testing being carried out in a number of countries worldwide (4-6), to date resistance to oseltamivir has only been detected occasionally in community cases of the new influenza A(H1N1)2009 viruses that emerged in the pandemic and displaced the former A(H1N1). In most cases, oseltamivir resistance developed during treatment with the drug, often in patients with known increased-risk factors for the emergence of resistant viruses, notably immunosuppression (7). Almost all resistant viruses reported to date have not transmitted efficiently from person-to-person (8, 9). In addition to sporadic cases (10), a few clusters of variable size have been reported in Viet Nam, Europe and USA where person-to-person transmission is likely to have occurred (11, 12, 13). These clusters usually involved vulnerable populations composed mostly of individuals who, for various reasons, were both more likely to develop resistance if treated with oseltamivir and to be infected if exposed to an influenza virus. The cluster of seven cases of oseltamivir-resistant A(H1N1)2009 viruses reported in 2009 in Viet Nam was the first known incidence of a resistant 2009 pandemic virus that was almost certainly transmitted person-to-person among otherwise healthy individuals (13).

In Europe, specifically in the UK, during the 2010–2011 influenza season, routine surveillance found some resistant cases, with no known exposure to oseltamivir in community settings (14).

Based on the reports in the European Surveillance System (TESSy) for the influenza season of 2010–2011, 2 562 A(H1)2009, 100 A(H3) and 508 influenza B viruses have been screened for resistance to neuraminidase inhibitors. Of these, 117 A(H1)2009 viruses were resistant, with the bulk of them being detected in the UK (58), Denmark (27) and France (12). All viruses tested remained sensitive to zanamivir. In terms of adamantane sensitivity, all A(H1)2009 and A(H3) viruses (261 and 53 screened, respectively) were resistant (15).

Event background information

On 29 August 2011, the state of New South Wales in Australia reported the presence of the H275Y amino acid substitution in the neuraminidase proteins of a cluster of pandemic A(H1N1)2009 influenza cases (16, 17).

Out of 184 samples tested between June and August 2011 by the WHO Collaborating Centre (CC) for Reference and Research on Influenza in Australia, 25 (13.6%) showed the presence of the associated amino acid substitution in the neuraminidase protein, indicating resistance to the neuraminidase inhibitor oseltamivir and reduced susceptibility to peramivir. None of the 16 cases for whom epidemiologic/clinical information is available reported having taken oseltamivir before sampling. All but two of the reported cases live close (50 km radius) to the centre of Newcastle, New South Wales, in the region of Hunter New England. The viruses from the oseltamivir resistance cluster described in New South Wales do not exhibit any resistance to zanamivir.

In comparison, only two other oseltamivir-resistant viruses have been detected in Australia this year. These were isolates from Brisbane, Queensland, and Perth, Western Australia from January and March 2011 respectively, with no further cases detected.

Oseltamivir-resistant strains continue to be detected at a similar frequency in the most recent specimens from the Newcastle, New South Wales region in August 2011, although influenza activity is declining in the region. Early genetic analyses at the WHO Collaborating Centre (CC) for Reference and Research on Influenza in Australia indicate that the haemagglutinin and neuraminidase genes of the resistant viruses are closely related. Further analyses as well as additional testing of specimens from the nearby Sydney region are in progress.

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The presence of the gene mutation conferring H275Y substitution in the neuraminidase is well recognised and known to have been widely prevalent in the former seasonal A(H1N1). So far, its presence in the new pandemic A(H1N1)2009 viruses has been limited. The current occurrence of the geographic cluster of oseltamivir-resistant cases in Australia, without a history of oseltamivir intake or presence of immunosuppression, is therefore an important observation which could have a potential public health impact. However, similar community cases were observed in the European winter of 2010–2011.

The probable transmission of the resistant virus from person-to-person in this cluster indicates some circulation in the local community. While the cluster has remained localised, it cannot be assumed that the variant virus will not become more widespread. If spread does occur, there will be implications for prophylaxis and treatment of influenza patients.

Monitoring of antiviral resistance is ongoing in Europe and in the 2009–2010 season some oseltamivir resistance was found among A(H1N1)2009 viruses. This included some cases with no evidence of exposure to oseltamivir in the infected person, as is the case in Australia. Hence the Australian findings are not new for Europe. It is likely that with the current level of oseltamivir use in Europe oseltamivir-resistant influenza viruses will be detected occasionally in vulnerable patients in hospital settings. In addition, oseltamivir-resistant viruses may evolve from time to time without the pressure of antiviral treatment. However, it is difficult to predict if viruses resistant to oseltamivir will become dominant in the near future, as happened in 2007–2008 with the former seasonal A(H1N1) influenza. As has been shown for the former seasonal A(H1N1), additional amino acid substitutions in the neuraminidase and haemagglutinin proteins were needed for established community circulation.

As advised earlier by WHO for A(H1N1) 2009 pandemic viruses (4), epidemiological investigations focusing on cases of NAI-resistant viruses are continuing in Europe. Given the experience with the former seasonal A(H1N1) influenza in 2007–2008 this is of the utmost importance when developing guidance for the prophylactic and treatment use of NAIs targeting influenza.

Conclusions and recommendations

The occurrence of the neuraminidase gene mutation (conferring H275Y substitution in the neuraminidase glycoprotein) in a cluster of cases in Australia, with neither a history of oseltamivir intake before testing nor immunosuppressed status, is of public health importance. Only ongoing surveillance will indicate whether this occurrence remains a localised event or whether it has the potential to become widespread. At present, the risk of this cluster becoming more widespread and having public health implications is low. However, if spread does occur, the consequences for public health in Europe will need to be considered.

Surveillance for the occurrence of resistant viruses will be essential, both during and after the upcoming influenza season in the northern hemisphere. Particular attention must be given to detecting transmission of resistant viruses which will mean gathering data on prior antiviral exposure. This will be important to ensure correct, targeted treatments, specifically for cases with severe influenza-related illness.

Since the A(H1N1)2009 virus antigen is included in the recommended seasonal flu vaccine for the coming season this potential for emergence of oseltamivir resistance is yet another reason why EU citizens, for whom vaccination is recommended by Member States, should accept the offer.

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References

1. McKimm-Breschkin J, Trivedi T, Hampson A, Hay A, Klimov A, Tashiro M, et al. Neuraminidase sequence analysis and susceptibilities of influenza virus clinical isolates to zanamivir and oseltamivir. *Antimicrob Agents Chemother.* 2003 Jul;47(7):2264-72. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC161875/pdf/1125.pdf>
2. Hurt AC, Ernest J, Deng YM, Iannello P, Besselaar TG, Birch C, et al. Emergence and spread of oseltamivir-resistant A(H1N1) influenza viruses in Oceania, South East Asia and South Africa. *Antiviral Res.* 2009 Jul;83(1):90-3. Available at: http://www.sciencedirect.com/science?_ob=MIImg&_imagekey=B6T2H-4VXB6XY-2-5&_cdi=4919&_user=4512315&_pii=S0166354209002782&_origin=&_coverDate=07%2F31%2F2009&_sk=999169998&_view=c&_wchp=dGLzVlb-zSkWb&_md5=641d7c0ac37a0972bb0b48b4c1c3335a&_ie=/sdarticle.pdf
3. Hauge SH, Dudman S, Borgen K, Lackenby A, Hungnes O. Oseltamivir-resistant influenza viruses A (H1N1), Norway, 2007–08. *Emerg Infect Dis.* 2009 Feb;15(2):155-62. Available at: <http://www.cdc.gov/eid/content/15/2/pdfs/08-1031.pdf>
4. WHO. Oseltamivir-resistant pandemic (H1N1) 2009 influenza virus, October 2009. *Wkly Epidemiol Rec.* 2009 Oct 30;84(44):453-9. Available at: <http://www.who.int/wer/2009/wer8444.pdf>
5. CDC. Flu View, 2009–2010 Influenza Season, Week 47 ending 28 November 2009. Available at: <http://www.cdc.gov/flu/weekly/weeklyarchives2009-2010/weekly47.htm>
6. ECDC. Weekly influenza surveillance overview, December 11, 2009. Available at: http://www.ecdc.europa.eu/en/activities/surveillance/EISN/Newsletter/091211_EISN_Weekly_Influenza_Surveillance_Overview.pdf
7. Calatayud L, Lackenby A, Reynolds A, McMenamin J, Phin N, Zambon M, et al. Oseltamivir-resistant pandemic (H1N1) 2009 virus infection in England and Scotland, 2009–2010. *Emerging Infectious Diseases.* 2011. Available at: <http://www.cdc.gov/eid/content/17/10/pdfs/11-0117.pdf>
8. ECDC. Public health development: oseltamivir-resistant pandemic (H1N1) 2009 influenza virus, October 2009. 2009. Available at: http://www.ecdc.europa.eu/en/activities/sciadvice/Lists/ECDC%20Reviews/ECDC_DispForm.aspx?List=512ff74f%2D77d4%2D4ad8%2Db6d6%2Dbf0f23083f30&ID=683&RootFolder=%2Fen%2Factivities%2Fsciadvice%2FLists%2FECDC%20Reviews
9. Meijer A, Jonges M, Abbink F, Ang W, van Beek J, Beersma M, et al. Oseltamivir-resistant pandemic A(H1N1) 2009 influenza viruses detected through enhanced surveillance in the Netherlands, 2009–2010. *Antiviral Res.* 15 Jul 2011. Available at: <http://www.sciencedirect.com/science/article/pii/S0166354211003718>
10. Hurt AC, Deng YM, Ernest J, Caldwell N, Leang L, Iannello P, et al. Oseltamivir-resistant influenza viruses circulating during the first year of the influenza A(H1N1) 2009 pandemic in the Asia-Pacific region, March 2009–March 2010. *Euro Surveill.* 2011;16(3). Available at: <http://www.eurosurveillance.org/images/dynamic/EE/V16N03/art19770.pdf>
11. CDC. Oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection in two summer campers receiving prophylaxis--North Carolina, 2009. *MMWR Morb Mortal Wkly Rep.* 11 Sep 2009;58(35):969-72. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mmm5835a1.htm>
12. HPA. HPA statement on possible transmission of oseltamivir resistant pandemic influenza A(H1N1) 20 November 2009. Available at: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1258560561316?p=1231252394302
13. Mai LQ, Wertheim HF, Tran ND, van Doorn HR, Nguyen TH, Horby P. A community cluster of oseltamivir-resistant cases of 2009 H1N1 influenza. *N Engl J Med.* 7 Jan 2010;362(1):86-7. Available at: <http://www.nejm.org/doi/pdf/10.1056/NEJMc0910448>
14. Lackenby A, Moran Gilad J, Pebody R, Miah S, Calatayud L, Bolotin S, et al. Continued emergence and changing epidemiology of oseltamivir-resistant influenza A(H1N1)2009 virus, United Kingdom, winter 2010–11. *Euro Surveill.* 2011;16(5). Available at: <http://www.eurosurveillance.org/images/dynamic/EE/V16N05/art19784.pdf>
15. ECDC. Weekly Influenza Surveillance Overview weeks 32–33, 2011. Available at: http://ecdc.europa.eu/en/publications/Publications/110826_SUR_Weekly_Influenza_Surveillance_Overview.pdf

16. Promed. Influenza (50) Australia (New South Wales), H275Y mutation cluster. 2011. Available at:
http://www.promedmail.org/pls/otn/f?p=2400:1202:3081320084688062::NO::F2400_P1202_CHECK_DISPLAY,F2400_P1202_PUB_MAIL_ID:X,89966
17. Government N. Influenza Update – antiviral resistance seen in New South Wales 2011. Available at:
<http://www.health.nsw.gov.au/publichealth/infectious/index.asp>