

ECDC/WHO FAQs for Oseltamivir Resistance

Q1. How did WHO, the European Commission, the ECDC (European Centre for Disease Prevention and Control) and the European Medicines Agency learn about oseltamivir resistance in influenza viruses?

A1. The Norwegian authorities notified their EU partners, and WHO via the International Health Regulations (IHR) mechanism and the European Early Warning and Response System (EWRS), on 25 January 2008 about a high rate of resistance to an antiviral drug, oseltamivir (Tamiflu®) in seasonal influenza A(H1N1) viruses. Of 16 virus isolates tested, 12 (75%) were resistant to oseltamivir. All the viruses were collected from patients at the start of the influenza season in November and December 2007 in Norway.

Q2. Has oseltamivir resistance been found in other countries this influenza season?

As of 25th January, the European Surveillance Network for Vigilance Against Viral Resistance (VIRGIL), the WHO Collaborating Center, MRC National Institute for Medical Research in London and the European Influenza Surveillance Scheme (EISS) had reported that approximately 13% of around 150 H1N1 isolates from across Europe have shown resistance. Norway showed the highest proportion (over 70%) of resistant isolates, while much lower rates of resistance were found in viruses tested from France, the United Kingdom and Denmark. Testing is now underway from other countries.

WHO is seeking further information from participants in its Global Influenza Surveillance Network (GISN) to assess the extent of circulation of oseltamivir-resistant viruses. GISN is a worldwide network of laboratories including National Influenza Centers (NICs) and Collaborating Centers (CCs) that collect and analyze thousands of viruses each year. From what WHO has learned so far, none of the H1N1 isolates tested by the WHO CC in Tokyo or by China's Special Administrative Area of Hong Kong NIC were oseltamivir resistant last season (2006-7) or during the early part of the current season. The Centers for Disease Control and Prevention in the United States have reported a 5% prevalence of resistance in H1N1 samples tested to date. These preliminary data indicate that oseltamivir resistance in H1N1 viruses is geographically variable but not limited to Europe. However, the distribution globally is yet not clear.

Q3. Have other types of influenza viruses tested resistant to oseltamivir?

A3. The elevated resistance to oseltamivir appears currently limited to seasonal H1N1 viruses and does not involve circulating H3N2 or influenza B viruses. All of the resistant H1N1 viruses in Europe have a specific resistance mutation in the viral neuraminidase (i.e., a histidine to tyrosine substitution at amino acid 274). Influenza H1N1 is the predominant influenza A virus currently circulating in many countries in Europe and other parts of the northern hemisphere this season but in other countries, influenza A H3N2 or a mixture of A and B viruses are predominant.

Q4. Is this a new problem?

A4. Resistance to oseltamivir in influenza viruses circulating in the community has been found before but at much lower levels. The high percentage of resistance to oseltamivir among circulating influenza viruses is new. Past surveillance studies have found rates typically ranging from 0% to <0.5%. The highest rate of oseltamivir resistance that had been reported previously for surveillance of community isolates was in Japan during 2005-06 when 2.2 % of 178 H1N1 isolates were found to be resistant. During the last winter season (2006-7), no resistant H1N1 variants were detected in isolates from Japan or Europe, and less than 1% of U.S. H1N1 isolates showed oseltamivir resistance.

However, oseltamivir resistance is well-documented to emerge in persons being treated with the drug. In clinical studies, H1N1 viruses with this particular mutation have been detected in up to 16% of H1N1-infected children treated with oseltamivir. Typically, the resistant strains have emerged 3 to 6 days after treatment was begun but were not detected a few days later.

Q5. Did resistance develop because patients in Norway and other countries were taking oseltamivir?

A5. None of the patients in Norway or elsewhere in Europe were reported either to have taken oseltamivir or have been exposed to people who had taken oseltamivir. The lack of drug treatment is not unexpected since oseltamivir is not often prescribed by doctors in most European countries.

Q6. Is there an explanation for the high frequency of oseltamivir resistance?

A6. The frequency of oseltamivir resistance in H1N1 viruses in the current influenza season is unexpected and the reason why a high percentage of these viruses are resistant is currently unknown. Available information does not indicate selective drug pressure is driving the development of resistance since few of the patients are known to have taken oseltamivir. Influenza viruses are continuously changing and it is possible that a resistant strain has emerged spontaneously. Further detailed laboratory characterization of circulating H1N1 viruses and epidemiological information on patients will be needed to help answer this question.

Q7. Did the patients with resistant viruses have any links to one another?

A7. No. Preliminary investigation so far suggest that most of the persons with resistant viruses were not in contact or linked in any known way. Patients were not limited to a particular geographic location in a country. In general, patients in Norway were not known to have traveled to other countries before becoming ill. These findings are consistent with this virus strain circulating at community level in some European countries.

Q8. What sort of illness has been associated with the resistant viruses?

A8. There is no evidence that the resistant viruses are causing more severe illness than other influenza viruses. Information is limited at present, but the Norwegian patients appear to have had typical influenza illness. Three of them were hospitalized and later discharged. As for the other seasonal influenza viruses, also the ones with Oseltamivir resistance can cause severe disease and fatalities among vulnerable people such as infants and the elderly. However, influenza seasons in which H1N1 viruses predominate typically are associated with less severe illness and lower mortality overall than seasons in which H3N2 viruses are predominant.

Q9. How easily are oseltamivir resistant viruses transmitted between people?

A9. The available evidence indicates that these oseltamivir-resistant H1N1 viruses are transmissible from one person to another, but there is no evidence that the resistant H1N1 viruses are more transmissible between people than non-resistant viruses. Past studies in Japan suggested that low-level community transmission may occur with H1N1 viruses possessing the same resistance mutation that has been found in these recent cases. H1N1 viruses with this mutation are transmissible between laboratory animals.

Q10. How does resistance affect oseltamivir's activity against the influenza virus?

A10. Oseltamivir is an antiviral drug that blocks influenza viruses from spreading in the respiratory tract. The current resistant H1N1 viruses have been found to contain a specific mutation that makes them highly resistant to oseltamivir. This means that oseltamivir would most likely be ineffective for treating or preventing infections caused by these resistant H1N1 strains, although the drug will be effective against other influenza virus infections.

Q11. Are there other drugs that can be used to treat oseltamivir resistant H1N1 virus infection?

A11. To date the oseltamivir-resistant H1N1 isolates this season have been fully susceptible to the other available antiviral drugs, zanamivir and the adamantanes (amantadine and rimantadine). These would be alternative drugs for prevention or treatment of oseltamivir-resistant H1N1 infections. However, in many parts of the world, influenza viruses are now resistant to the adamantane drugs.

Q12. Is this season's influenza vaccine effective against oseltamivir resistant strains?

A12. The antiviral susceptibility and influenza vaccine effectiveness are based on different mechanisms. The oseltamivir resistance mutation does not affect the vaccine effectiveness. So far this influenza season, A(H1N1) viruses is predominant in most parts of northern hemisphere, and the majority are antigenically similar to A/Solomon Islands/3/2006, a vaccine virus. Immunization with this season's vaccine remains an effective means of prevention against illness due to influenza viruses, including the oseltamivir-resistant H1N1 variants.

Q13. Do the oseltamivir resistant viruses pose any risk to cause a pandemic?

A13. No, human seasonal H1N1 viruses, including those with a resistance mutation, do not have the potential to cause a pandemic. The current type of human H1N1 viruses have been circulating widely in the population for many years without leading to a pandemic.

Q14. What potential implications could the findings of oseltamivir resistance among seasonal viruses have for the treatment of H5N1 cases?

A14. Oseltamivir resistance due to the same mutation has been reported in three patients with H5N1 infection who were treated with oseltamivir. There are no reports of persons acquiring H5N1 infection from a patient with an oseltamivir resistant H5N1 virus.

Q15. What implications does oseltamivir resistance in seasonal H1N1 viruses have for the avian influenza H5N1?

A15. The implications are uncertain at this point. The neuraminidase protein in human H1N1 viruses is different from that in avian H5N1 viruses. Until we learn why the unexpected increase in oseltamivir resistance has occurred in H1N1 viruses, it is too early to know what, if any, potential there might be for a similar increase in resistance to occur in H5N1 viruses. Furthermore, H5N1 viruses have not shown the ability to spread efficiently from person-to-person. WHO has not changed any of its recommendations regarding H5N1 treatment and preparations.

Q16. What is being done about the situation?

A16. WHO, the European Commission and ECDC and other organizations worldwide are working together to gather additional information on antiviral resistance in H1N1 viruses. The Collaborating Centers in WHO's Global Influenza Surveillance Network (GISN) and the VIRGIL Network perform testing and share the results of antiviral susceptibility data on seasonal human viruses and H5N1 isolates. WHO is also consulting with a variety of experts to assess the public health implications of these findings and the possible need for additional guidance. ECDC has published an interim Risk Assessment, which is available at: http://ecdc.europa.eu/pdf/080127_os.pdf. WHO, the European Commission and ECDC will continue to collaborate in monitoring the situation carefully, seeking advice from experts, and providing updated information as it becomes available.

Q17. What is going to happen? Is the oseltamivir resistant strain of H1N1 likely to become the predominant strain of H1N1 worldwide this influenza season?

A17. It is simply too early to know. Information to date indicates that the resistant virus is transmissible from person to person. However, the prevalence of resistant viruses varies widely in European countries and they are predominant only in Norway at present. Previous laboratory studies have found that influenza viruses with this specific resistance

mutation can transmit from one animal to another but may not be as infectious when compared with the non-resistant "parent" virus. Thus, it is possible that the resistant strain will not become more common in other countries. Careful monitoring will be required throughout the rest of the season to follow the situation globally.

Q 18. How can I protect myself and my family from seasonal influenza?

A18. Seasonal influenza vaccination is the primary means of influenza prevention.

Following national guidance, people in high-risk groups for influenza complications (i.e. older persons, those with chronic conditions, etc) should get vaccinated against influenza, if they have not already done so.

- Seasonal vaccines are effective for those who wish to reduce their risk of influenza and some countries advise use in travelers to influenza-affected countries.

People can also take steps to reduce the spread of influenza:

- Where possible, people infected with influenza should avoid close contact with others
- Basic hygiene measures, particularly covering coughs and sneezes and hand-washing, are likely effective in reducing the spread of influenza

Antiviral drugs that are active against seasonal influenza viruses, including the resistant H1N1 virus, are available in many countries.

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