

Oseltamivir-resistant pandemic (H1N1) 2009 influenza case and cluster investigation



Introduction

As with all outbreaks, the local outbreak control plan will be followed. Additional advice can be requested from the Health Protection Agency Centre for Infections.

The mutation associated with oseltamivir resistance is the H275Y mutation on the N1 neuraminidase of the pandemic virus. This is the most common type of mutation associated with oseltamivir resistance.

If a case of oseltamivir-resistant pandemic (H1N1) 2009 influenza should be detected, by either an HPA regional laboratory or the reference laboratory at the Centre for Infections, then the health protection unit (HPU) will be informed as soon as possible.

On being informed of a case, a number of issues need to be considered and it will be essential that the case is investigated according to attached HPA protocol using the standard questionnaire (Appendix 1 and 2 respectively).

Risk assessment

On being informed of a case of oseltamivir-resistant pandemic (H1N1) 2009 influenza, the HPU should undertake a documented risk assessment to determine the likelihood that the case is associated with transmission of resistant virus, the extent of transmission and so inform public health action.

The risk assessment will help to determine the extent and scope of any public health measures. The risk assessment should be reviewed regularly as new information and data are acquired.

The HPA questionnaire can be used to gather the appropriate clinical and epidemiological information. The following issues need to be considered:

- 1 Consider details of the case and whether linked to other known cases. The reference and regional virology laboratories may be able to provide some information on previous specimens that may be linked in time and place.
- 2 Assess whether the case has been treated with oseltamivir. It will be particularly important to determine whether the swab was taken before or after treatment with oseltamivir, as this may indicate whether transmission of a resistant virus has taken place or whether resistance has been acquired during treatment.
- 3 Consider whether the patient has any co-morbidities, particularly immunosuppression. Antiviral resistance appears to emerge more frequently in this group because of high viral replication and prolonged shedding.
- 4 Consider the setting and population at risk. Most cases of oseltamivir resistance have arisen in hospitalised patients, particularly those with underlying immunosuppression or chronic respiratory disease. The majority of cases have acquired oseltamivir resistance

while on treatment with oseltamivir. The risk of transmission is higher in hospital settings, with exposure being more likely and the people exposed more vulnerable to influenza virus. The risk assessment should consider the extent of exposure in the setting, including the isolation facilities and the infection control methods used, such as personal protective equipment.

- 5 Assess whether there has been any foreign travel in the week before onset. This may need to be reported to WHO under international health regulations.

Management of cases

- 6 Initial assessment of household and close contacts of confirmed cases. Establish a line list of contacts to be monitored, any underlying illness, previous or current symptoms of influenza and any medicine prescribed:
 - a) Household and other close contacts. In household settings, household and close contacts should be asked about recent symptoms of influenza-like illness and about any underlying medical conditions which may put them at greater risk from pandemic influenza. They should contact the HPU if symptoms develop.
 - b) Contacts in other settings, including hospital ward, nursing or residential home, or residential school. In healthcare or other settings, arrangements to monitor contacts for development of new symptoms should be made.

The initial surveillance will assist in assessing risk of transmission with a number of linked confirmed cases and possible (symptomatic) cases.

Continued surveillance of contacts after exposure will enable a dynamic risk assessment to be done and proportionate control measures implemented.

- 7 Infection control measures and personal hygiene. Control measures would normally include isolation while there are still viruses detectable in the respiratory tract, appropriate use of personal protective equipment and good hand and respiratory hygiene.
- 8 Maintain isolation and hygiene measures until virological clearance. People who are immunocompromised can continue to shed the virus and be infectious for prolonged periods. They should maintain isolation, where possible at home, or if in a healthcare setting until two viral swabs are negative, 48 hours apart. The need for ongoing viral testing and the frequency of any testing should be discussed with the local microbiologist or virologist.
- 9 Treatment of possible cases (after testing for H1N1). Symptomatic contacts of a case of confirmed oseltamivir-resistant H1N1 influenza should be treated in accordance with local protocols. Nose and throat swabs should be taken before starting treatment and urgent

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virological testing including antiviral resistance testing organised with the regional virology laboratory. Infection control measures will be needed until the diagnosis has been ruled out, following negative testing or until clinical recovery.

Management of contacts

- 10 Prophylaxis of close contacts with serious underlying conditions. Close contacts with a serious underlying illness should be offered post-exposure prophylaxis with zanamivir.
- 11 Prophylaxis of household and contacts in order to contain the spread of oseltamivir-resistant pandemic (H1N1) 2009 influenza may be considered and advice from the Centre for Infections should be sought before any decision is made. If there is evidence of sustained transmission, a risk assessment may lead to widespread post-exposure prophylaxis, in order to halt further transmission. The risk assessment would weigh the need for a number of people who would require antiviral prophylaxis against the expected benefit of halting further transmission. A decision to offer prophylaxis to large numbers of people would be taken with expert virological and epidemiological advice.
- 12 Vaccination in the outbreak setting. Influenza immunisation will not provide protection until 10-14 days after immunisation. Therefore, in an acute outbreak, vaccination may have little benefit. However, it is currently recommended that healthcare staff and household contacts of patients who are immunocompromised should be offered vaccination with the pandemic vaccine. This may play a key role in preventing outbreaks from occurring, or preventing a prolonged outbreak among a large and vulnerable population. Vaccination of these groups should be actively promoted.

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Appendix 1

Oseltamivir resistance of pandemic (H1N1) 2009 influenza in the UK, 2009-2010

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Summary

Since January 2008 an increase in the number of seasonal A/H1N1 cases resistant to oseltamivir has been reported by different countries. In the UK the monitoring of influenza antiviral susceptibility was first implemented in 2006 and, during the season 2008-2009, a specific study was conducted to determine the clinical and epidemiological characteristics of A/H1N1 resistant cases. Since then the ongoing influenza pandemic has led to changes in the recommendation of prescribing antiviral drugs for treatment and prophylaxis. The emergence of a transmissible oseltamivir-resistant influenza strain would have significant implications for the management of cases and may lead to the need to adapt the current recommendations regarding the use of antiviral drugs.

1. Introduction

Since January 2008 52 countries and territories (the majority being from the European region) reported to WHO an increase in the number of A/H1N1 virus carrying a specific neuraminidase mutation (H275Y)ⁱ. This mutation confers high-level resistance to oseltamivir. Previously, such resistance was rarely observed (less than 1% prevalence during the winter season 2006/2007 in the northern hemisphere). The influenza strains with this mutation had arisen infrequently after treatment in clinical trials of oseltamivirⁱⁱ. A prevalence of 11% of oseltamivir resistance in the UK was reported during the 2007/2008 season and 98% of the seasonal influenza A/H1N1 cases were resistant to oseltamivir in 2008/2009.

The surveillance of an oseltamivir resistant strain in the UK during the 2007-2008 season suggested it was similar to other influenza strains, in term of the age groups affectedⁱⁱⁱ. However, immunosuppressed cases are likely to have repeated doses of antivirals and have prolonged shedding of virus.

Previously, usage of oseltamivir in Europe was not reportedly high; however, recommendations have changed since the beginning of the influenza pandemic. In the UK from April to July 2009, during the containment phase, antiviral treatment was offered to suspected cases and antiviral prophylaxis to close contacts of confirmed and suspected cases. Since July 2009 the management of pandemic influenza has moved to a treatment-only phase with prophylaxis offered to only high-risk contacts^{iv}.

The emergence of a transmissible oseltamivir-resistant influenza strain would have significant implications for the current management of cases and may lead to the need to

adapt the current recommendations regarding the use of antiviral drugs. This protocol outlines the epidemiologic and public health requirement need for early detection of an oseltamivirosetamivir-resistant H1N1 case.

2. Aim and specific objectives

2.1 Aim

To determine the epidemiologic, clinical and demographic characteristics of pandemic (H1N1) 2009 influenza oseltamivir-resistant cases and identify evidence of possible transmission of resistant strain to close contacts during the 2009/2010 season in the UK, in order to inform prevention and control measures.

2.2 Specific objectives

To determine the clinical features of pandemic (H1N1) 2009 influenza oseltamivir-resistant cases.

To determine the severity of disease of pandemic (H1N1) 2009 influenza oseltamivir-resistant cases.

To compare epidemiologic, clinical (including outcome) and demographic characteristics of virologically confirmed patients with pandemic (H1N1) 2009 oseltamivir-resistant influenza to seasonal A/H1N1 oseltamivir-resistant influenza cases.

To identify evidence of possible transmission of pandemic (H1N1) 2009 influenza resistant strain from and to close household and non-household contacts.

To identify risk factors for transmission of pandemic (H1N1) 2009 influenza resistant strain.

3. Method

3.1 Study design

A descriptive study of pandemic (H1N1) 2009 influenza oseltamivir-resistant cases and their close contacts will be conducted.

An analytical study will be implemented to compare characteristics of resistant pandemic (H1N1) 2009 influenza and resistant seasonal A/H1N1 2008 cases.

3.2 Study population

All patients, in the UK, detected by the influenza surveillance system and confirmed with oseltamivir-resistant pandemic (H1N1) 2009 influenza by the HPA Virus Reference Division (VRD) during the period 1 April 2009 to 30 April 2010.

3.3 Case definition

A pandemic (H1N1) 2009 influenza oseltamivir-resistant case is one detected by the influenza surveillance system, whose pandemic (H1N1) 2009 influenza is virologically confirmed by the HPA VRD laboratory during the period 1 April 2009 to 30 April 2010 and tested resistant to oseltamivir.

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A seasonal 2008 oseltamivir-resistant influenza A/H1N1 case is a case detected by the influenza surveillance system, whose influenza A/H1N1 is virologically confirmed by the HPA VRD laboratory during the period 1 October 2008 to 30 April 2010 and tested resistant to oseltamivir.

A household close contact is defined as any person who lives in the same household as the case and who had at least one overnight stay in the household after the onset of illness in the case.

A non-household close contact is defined as:

- Any person who had more than one hour of unprotected (that is, not wearing a mask or respirator) face-to-face contact (that is, within touching or speaking distance) with a case while the case had symptoms of influenza.
- Any individuals who provided informal care to the case, coming within speaking distance (<1 metre) while the case had symptoms of influenza.
- Any health or social care workers who provided direct clinical or personal care or who examined a case while the case had symptoms of influenza.

3.4 Data collection, sources of information, transmission of information

Data collected

Biological, demographic, epidemiological and clinical data will be collected:

Microbiological data

- Date of sampling and date of receipt.
- Influenza subtyping.
- Genotypic confirmation of oseltamivir susceptibility.
- Phenotypic confirmation of oseltamivir and zanamivir susceptibility, if available.

Demographic and epidemiological data

- Patient name, sex and date of birth.
- Recent travel history.

Clinical data

- Date of onset.
- Symptoms.
- Complications.
- High-risk group according to Department of Health definition (including immunosuppression).
- Disease progression.
- Prophylaxis and treatment (including doses and number of courses).

Exposure

- Travel history.
- Exposure to cases presented with influenza-like illness symptoms.

Transmission to close contacts

- Number of close contacts.
- Evidence of secondary transmission.

The following data will be used for patient identification and to contact the clinician:

- Laboratory name and location.
- Sample identifier and MOLIS number.
- Patient NHS number.
- Clinician name and contact details.

Data sources

Microbiological data

Biological samples collected from the suspect cases by the sentinel GP, hospitals and HPA or NHS laboratories are sent to the virus reference laboratory for subtyping and antigenic characterisation.

Screening for resistance to neuraminidase inhibitor drugs oseltamivir and zanamivir is performed.

The virological information and the details from the A/H1N1 resistant cases (name and date of birth) and the laboratory name will be reported by VRD to the influenza/respiratory virus section, HPA Centre for Infections, as new cases are detected.

Demographic, epidemiological and clinical data

Demographic, epidemiological and clinical data from the cases and their close contacts will be directly collected by the local HPUs, or the HPA Centre for Infections by phone from the laboratory, and/or clinicians (GPs or hospital clinicians). A similar questionnaire will be used for all cases.

The local HPU will also be informed of the case.

Data management

Epidemiological and biological information will be stored in a shared EpiData database.

Data will be imported into an EpiData database to perform the descriptive analysis.

4. Confidentiality

Individual patient information will only be used when absolutely necessary^{vi}. For the analysis, all cases will be anonymised.

The EpiData database set up for follow-up of cases will be stored on password-protected computers at the HPA Centre for Infections.

5. Data collected

Microbiological data:

- Date of sampling and date of receipt.
- Influenza subtyping.
- Genotypic confirmation of oseltamivir susceptibility.
- Phenotypic confirmation of oseltamivir and zanamivir susceptibility, if available.

Demographic and epidemiological data:

- Patient name, sex and date of birth.,
- Recent travel history (four previous days): date and place.

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Clinical data

- Date of onset.
- Symptoms: fever, rhinorrhoea, pharyngitis, conjunctivitis, bronchitis, bronchiolitis, pneumonia, cough, dyspnoea, other symptoms.
- Complications: pneumonia, otitis media, encephalitis, ITU admission, other complications.
- High-risk group according to Department of Health definition: chronic respiratory disease, chronic heart disease, chronic renal disease, chronic liver disease, chronic neurological disease, diabetes mellitus, immunosuppression because of disease or treatment.
- Disease progression: uncomplicated, complicated, hospitalisation (duration), death (cause of the death).
- Prophylaxis and treatment: vaccination status for the current vaccine and date of vaccination; exposure to oseltamivir or other antiviral drugs (zanamivir, amantadine), dates and doses received; number of courses (personal exposure or contact with someone exposed in the household).
- Transmission: number of close contacts, number of cases among close contacts (date of onset of symptoms, last contact with index case).

Exposure

- Travel history.
- Exposure to influenza-like illness cases (number of cases, relationship with the case, antiviral treatment or prophylaxis received, date of onset of symptoms, underlying medical condition).

Close contacts

- Number of close contacts.
- Number of close contact with influenza-like illness symptoms.
- Date of onset of symptoms.
- Date of last contact with index case.

Definition of close contacts: A household close contact is defined as any person who lives in the same household as the case and had at least one overnight stay in the household after the onset of illness in the case.

A non-household close contact is defined as:

- Any person who had more than one hour of unprotected (that is, not wearing a mask or respirator) face-to-face contact (that is, within touching or speaking distance) with a case while the case had symptoms of influenza.
- Any individuals who provided informal care to the case, coming within speaking distance (<1 metre) while the case had symptoms of influenza.
- Any health or social care workers who provided direct clinical or personal care or who examined a case while the case had symptoms of influenza.

6. References

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