ECDC THREAT ASSESSMENT

First isolation of a secondary oseltamivir-resistant A(H1N1)v strain in Denmark

01 July 2009

Source and date of request

Internal request following an EWRS message from Denmark health authorities.

Public health issue

Isolation of a mutant A(H1N1)v virus containing a genetic marker of resistance to oseltamivir.

Consulted experts

Internal experts.

Event background information

Event reported by Danish EWRS Focal point on 29 June 2009:

In the context of tracing contacts of a cluster of four cases infected with influenza A(H1N1)v, including two imported cases in Denmark, a female contact, who initially tested negative on PCR, was given prophylaxis with oseltamivir (75mg per day). Five days later, despite reportedly having complied with treatment, she developed flu-like symptoms and was tested positive for A(H1N1)v. Sequencing of the virus showed a single mutation H275Y (H274Y in N2 numbering system) in the neuraminidase gene. The presence of the resistance marker and the phenotypic (in vitro) resistance was confirmed by a WHO collaborating centre, UK. The virus is not a re-assortant and remains susceptible to zanamivir (another neuraminidase inhibitor). No other virus isolated as part of this cluster investigation, including the presumed source patient, showed the mutation.

Stockholm, July 2009

ECDC threat assessment for the EU

To date, community isolates of the A(H1N1)v virus related to the ongoing pandemic have been found sensitive to oseltamivir and zanamivir and resistant to adamantanes (M2 blockers). This event is the first observation of resistance to oseltamivir in a pandemic A(H1N1)v virus. Available epidemiological and virological data do not allow determining whether the resistant variant in Denmark arose in an already treated prior case and then transmitted to the patient with documented resistance or in the context of post-exposure prophylaxis. Importantly, based on clinical criteria, there is no evidence that the resistant virus has subsequently transmitted to other persons.

The mutation consists of the substitution of histidine to tyrosine at amino acid position 275 (H275Y) in the neuraminidase segment gene (position 274 in N2 numbering system). This mutation has been described in the past, associated with so-called secondary resistance to oseltamivir acquired during treatment of both H1N1 and H5N1 virus infections. In Japan, where the drug was used more commonly than in Europe[1], the mutation was detected in up to 16% of oseltamivir-treated children, perhaps associated with underdosing[2]. However, a recent study in the United Kingdom also confirmed emergence of resistant seasonal H1N1 viruses with this mutation in children treated with standard, approved doses[3].

Consequently, it is likely that such oseltamivir resistance mutation will be observed again in individuals taking oseltamivir (treatment or chemoprophylaxis). Furthermore, the theoretical possibility exists that oseltamivir-resistant neuraminidase might be acquired through reassortment in the future. The current event does highlight the increased likelihood of such event arising from widespread use of oseltamivir and the need for continued surveillance.

The affected patient recovered without complication. However, in more seriously ill patients, like in those with influenza viral pneumonia, the emergence of resistance might be associated with antiviral treatment failure. Of note, emergence of oseltamivir resistance in the context of treating H5N1 illness has been temporally associated with failure to clear virus and fatal outcome in two patients[4]. Such findings emphasise the importance of serial virologic sampling in severely ill patients whenever possible and monitoring for resistance when prolonged shedding of virus is detected.

Depending on the specific H1N1 virus studied, some past studies have shown that seasonal H1N1 virus containing this mutation may be less infectious, although still transmissible in ferrets[5] and reduced in replication and pathogenicity[6], as demonstrated in animal studies. However, oseltamivir-resistant A/Brisbane/59/2007-like viruses with this mutation have spread globally since the 2007–2008 season in the apparent absence of selective drug pressure and displaced other seasonal A(H1N1) viruses in most countries (98% resistance in EU in 2008–2009)[7]. These resistant seasonal H1N1 viruses are no less replication competent or virulent in humans than closely-related oseltamivir susceptible seasonal H1N1 viruses.

Thus, the effects of this H275Y mutation on neuraminidase function, viral replication, virulence, and transmissibility in animal models or humans depend on the specific N1 neuraminidase under study. These data need to be ascertained for the pandemic (H1N1) 2009 virus with this oseltamivir-resistant mutation.

Conclusions and recommendations

The emergence of resistance while on antiviral treatment is a well-recognised phenomenon in influenza viruses. Emergence of resistant viruses is always a concern for individual patients as well as for the potential public health threat that they pose if they retain sufficient transmissibility. Surveillance for emergence of resistant viruses in treated persons, particularly those with severe disease or immunocompromised status, and in community isolates is of importance for monitoring this potential clinical and public health problem in the context of the current H1N1 pandemic.

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References

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